Lipotropics, Other
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Agents in this class are indicated as adjuncts to dietary modifications for the treatment of various dyslipidemias.

Drug	Manufacturer	Indication(s)
Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitor		
bempedoic acid* (Nexletol™)[1]	Esperion	▪ As adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease (CVD) who require additional lowering of low-density lipoprotein cholesterol (LDL-C)
ACL Inhibitor/Cholesterol Absorption Inhibitor		
bempedoic acid/ ezetimibe* (Nexlizet™)[2]	Esperion	▪ As adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic CVD who require additional lowering of LDL-C
Apolipoprotein B Synthesis Inhibitor		
lomitapide (Juxtapid®)[3]	Aegerion	▪ Reduction of LDL-C, total cholesterol, apolipoprotein B (Apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to a low-fat diet and other lipid-lowering treatments
Bile Acid Sequestrants		
cholestyramine (Questran®, Questran Light)[4]	generic, Par	▪ Primary hypercholesterolemia ▪ Relief of pruritus associated with partial biliary obstruction
colesevelam† (Welchol®)[5]	generic, Daiichi Sankyo	▪ As adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia ▪ Reduction of LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) who are unable to reach LDL-C target despite adequate trial of dietary therapy and lifestyle modifications ▪ Glycemic control in adults with type 2 diabetes mellitus (T2DM)
colestipol (Colestid®)[6,7]	generic, Pfizer	▪ Primary hypercholesterolemia
Cholesterol Absorption Inhibitors		
ezetimibe (Zetia®)[8]	generic, Merck Sharp & Dohme	▪ Primary hypercholesterolemia (monotherapy or in combination with a statin) ▪ Mixed hyperlipidemia (in combination with fenofibrate) ▪ HoFH (adjunctive therapy in combination with atorvastatin or simvastatin) ▪ Homozygous familial sitosterolemia

* Limitations of use for both bempedoic acid (Nexletol) and bempedoic acid/ezetimibe (Nexlizet) include that the effect on cardiovascular (CV) morbidity and mortality has not been determined.

† Limitations of use for colesevelam (Welchol) include that (1) it should not be used to treat type 1 diabetes mellitus or diabetic ketoacidosis; (2) its effects on cardiovascular morbidity and mortality have not been established; (3) it has not been studied in T2DM in combination with a dipeptidyl peptidase 4 (DPP4) inhibitor; (4) it has not been studied in Frederickson Type I, III, IV, and V dyslipidemias; and (5) it has not been studied in children < 10 years of age or in premenarchal girls.

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FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Fibric Acids		
fenofibrate (Antara®)[9,10]	generic, Lupin	As an adjunct to diet: ▪ To reduce elevated LDL-C, total-cholesterol (Total-C), triglycerides (TG), and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia ▪ To treat adult patients with severe hypertriglyceridemia
fenofibrate (Fenoglide®)[11]	generic, Santarus	
fenofibrate (Lipofen®)[12]	generic, Kowa	
fenofibrate[13]	generic	
fenofibrate (Tricor®)[14]	generic, Abbvie	
fenofibrate (Triglide®)[15]	Casper	
fenofibric acid (Fibricor®)[16]	generic‡, Athena	▪ Primary hyperlipidemia or mixed dyslipidemia in adults ▪ Severe hypertriglyceridemia (≥ 500 mg/dL) in adults
fenofibric acid (Trilipix®)[17]	generic, Abbvie	▪ Primary hyperlipidemia or mixed dyslipidemia ▪ Severe hypertriglyceridemia
gemfibrozil (Lopid®)[18]	generic, Pfizer	▪ Hypercholesterolemia, Fredrickson type IIb (in patients without history of or symptoms of existing coronary heart disease (CHD) ▪ Hypertriglyceridemia, Fredrickson types IV and V hyperlipidemia
Niacin		
niacin ER (Niaspan®)[19]	generic, Abbvie	▪ Primary hyperlipidemia or mixed dyslipidemia ▪ Primary hyperlipidemia or patients with a history of coronary artery disease (CAD) and hyperlipidemia (in combination with a bile acid sequestrant) ▪ Severe hypertriglyceridemia as adjunct in patients at risk for pancreatitis ▪ Patients with a history of myocardial infarction (MI) and hyperlipidemia
niacin IR (Niacor®)[20]	generic, Avondale	▪ Primary hypercholesterolemia (monotherapy or in combination with bile-acid binding resin) ▪ Hypertriglyceridemia, types IV and V hyperlipidemia for those who present with a risk of pancreatitis (adjunctive therapy)
Omega-3 Fatty Acids		
icosapent ethyl§ (Vascepa®)[21]	Amarin	▪ As adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adults with elevated triglyceride (TG) levels (≥ 150 mg/dL) and – Established CVD or – Diabetes mellitus and ≥ 2 additional risk factors for CVD ▪ As adjunct to diet, to reduce TG levels in adults with severe hypertriglyceridemia (TG ≥ 500 mg/dL)
omega-3-acid ethyl esters§ (Lovaza®)[22]	generic, GlaxoSmithKline	▪ Treatment of hypertriglyceridemia in adults with TG ≥ 500 mg/dL

‡ Authorized generic (AG) available.

§ The effects of omega-3-acid ethyl esters on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia have not been determined. The effect of icosapent ethyl and omega-3-acid ethyl esters on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

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FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors		
alirocumab (Praluent®)[23]	Sanofi-Aventis	▪ To reduce the risk of myocardial infarction (MI), stroke, and unstable angina requiring hospitalization in adults with established atherosclerotic cardiovascular disease (ASCVD) ▪ As adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce LDL-C
evolocumab (Repatha®)[24]	Amgen	▪ As adjunct to diet, alone or in combination with other LDL-lowering therapies, for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C ▪ Treatment of patients with HoFH who require additional lowering of LDL-C as an adjunct to diet and other LDL-lowering therapies ▪ To reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD

The combination statin product, ezetimibe/simvastatin (Vytorin®), is not discussed in this review.

OVERVIEW

Many clinical trials have demonstrated that a high serum concentration of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) are major risk factors for coronary heart disease (CHD). The National Health and Nutrition Examination Survey (NHANES) reported that in 2015 to 2018, approximately 11.4% of adults in the United States (US) had high total cholesterol (≥ 240 mg/dL) and 17.2% had low HDL-C (< 40 mg/dL).[25] The prevalence of high total cholesterol was higher in women (12.1%) compared to men (10.5%), but the difference was not significant. The prevalence of low HDL-C was higher in men (26.6%) compared to women (8.5%). In 2015 to 2018, there were no significant race and Hispanic-origin differences in the prevalence of high total cholesterol in adults. The NHANES analysis was based on measured cholesterol only and does not consider whether lipid-lowering medications were taken. In addition, NHANES reported that the percentage of adults aged 20 and over with elevated triglycerides (TG) declined from 33.3% for 2001 to 2004 to 25.1% during 2009 to 2012.[26] In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA), in combination with the National Heart, Lung, and Blood Institute (NHLBI), released 4 new consensus guidelines regarding cholesterol management, cardiovascular (CV) risk assessment, obesity, and lifestyle. ACC/AHA emphasizes lifestyle modification, including a reduced calorie diet and aerobic physical activity, as a critical component of atherosclerotic cardiovascular disease (ASCVD) risk reduction, both prior to and in conjunction with cholesterol lowering drug therapies.[27,28,29,30]

There is a high level of evidence supporting the use of hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors ("statins") for secondary prevention and moderate to high level of evidence for their use for primary prevention.[31] As a class, they can lower LDL-C by ≥ 50% in a dose-related fashion. Statins typically have relatively minor effects on TG and high-density lipoprotein cholesterol (HDL-C) levels, reducing TG by 7% to 30% and increasing HDL-C by approximately 5% to 15%.[32]

Many non-statin therapies do not provide adequate ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.[33] As demonstrated in the AIM-HIGH

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study, the additional reduction in non-HDL-C (as well as apolipoprotein B [Apo B], lipoprotein (a) [Lp(a)], and triglycerides) levels with niacin therapy did not further reduce ASCVD risk in individuals treated to LDL-C levels of 40 to 80 mg/dL.[34] The ACCORD trial reported that, in diabetic patients with and without clinical CV disease, the addition of a fenofibrate to simvastatin therapy did not reduce the risk for CV events compared with simvastatin alone.[35] However, the ACC/AHA recognizes that maximally tolerated statin therapy might not be adequate to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C (≥ 190 mg/dL) at which time the addition of non-statin agents can be considered.[36] In contrast, the IMPROVE-IT study reported an average additional reduction in LDL-C of 17 mg/dL with the addition of ezetimibe to simvastatin.[37] The primary composite endpoint of CV death, myocardial infarction (MI), unstable angina, stroke, and coronary revascularization was significantly lower with combination therapy as compared to simvastatin alone (32.7% versus 34.7%, respectively; p=0.016). A significant reduction in MI and ischemic stroke and a nonsignificant increase in risk of hemorrhagic stroke were also reported with combination therapy.

In 2015, the FDA approved alirocumab (Praluent) and evolocumab (Repatha), a new class of lipotropic agents. Both are human monoclonal antibodies that bind to proprotein convertase subtilisin/kexin type 9 (PCSK9). The FOURIER (evolocumab; n=27,564) and ODYSSEY OUTCOMES (alirocumab; n=18,924) trials reported a 15% reduction in CV risk when evolocumab (Repatha) or alirocumab (Praluent) were added to optimal statin therapy.[38,39,40] LDL-C levels were reduced by 59% and 55% with each drug, respectively. In addition, the EBBINGHAUS cognitive function trial, a substudy of FOURIER, also demonstrated that evolocumab had no significant effect on cognitive function compared to placebo.[41,42]

Since the release of the 2013 guidelines for the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults, the ACC/AHA no longer supports the use of the National Cholesterol Education Program (NCEP) Expert Panel on Diagnosis, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) algorithm for risk assessment, citing that it is derived in an exclusively Caucasian sample population and focused on the limited scope of CHD alone.[43,44] Instead, they recommend use of the race- and gender-specific Pooled Cohort Equations to estimate 10-year ASCVD risk in both Caucasian and African American men and women.[45] They also no longer support a treat-to-target approach with goals such as LDL-C < 70 mg/dL and < 100 mg/dL for secondary and primary ASCVD prevention, respectively; rather, the guidelines advocate using the maximum tolerated statin intensity in patients identified to benefit from statin therapy and focus on treatments proven to reduce ASCVD events. The 2018 AHA/ACC guidelines on management of blood cholesterol, published along with several other relevant professional organizations, emphasized lifestyle therapies to review ASCVD risk.[46] The 2018 guidelines expanded upon the use of the 10-year ASCVD risk score and advise consideration of risk-enhancing factors, such as family history of premature ASCVD, persistent LDL-C ≥ 160 mg/dL, persistent triglycerides ≥ 175 mg/dL, metabolic syndrome, chronic kidney disease (CKD), history of preeclampsia or premature menopause, chronic inflammatory disorders, and high-risk ethnic groups, among others, when considering antilipid therapy. Coronary calcium score may also be used when uncertainty of level of ASCVD risk exists. For primary prevention, statins are recommended in patients with severe hypercholesterolemia and in adults 40 to 75 years of age with diabetes mellitus or at higher ASCVD risk. For secondary prevention, in very high-risk ASCVD patients (history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions), ACC/AHA considers addition of ezetimibe to maximally tolerated statin therapy a reasonable option when the LDL-C level

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remains ≥ 70 mg/dL; if LDL-C level still remains ≥ 70 mg/dL, then a PCSK9 inhibitor can be added. For LDL-C ≥ 190 mg/dL, high-intensity statin therapy is warranted regardless of ASCVD risk score. If LDL-C remains ≥ 100 mg/dL ezetimibe should be added, and if LDL-C is still ≥ 100 mg/dL and the patient has multiple risk factors, addition of a PCSK9 inhibitor may be considered.

High plasma HDL cholesterol (HDL-C) is associated with reduced risk of MI, but whether this association is causal is unclear. A study published in 2012 that utilizes databases of genetic information has found that raising HDL-C levels may not affect heart disease risk.[47] The study reported that carriers of the *LIPG 396Ser* allele (2.6% frequency) had higher HDL-C (0.14 mmol/L higher; $p=8\times10^{-13}$) but similar levels of other lipid and non-lipid risk factors for MI compared with non-carriers. This difference in HDL-C was expected to decrease risk of MI by 13% (odds ratio [OR], 0.87; 95% confidence interval [CI], 0.84 to 0.91), but the investigators found that the *396Ser* allele was not associated with risk of MI (OR, 0.99; 95% CI, 0.88 to 1.11; p=0.85). These data challenge the concept that raising HDL-C will uniformly translate into reductions in risk of MI.

The NCEP categorizes above normal serum TG levels as borderline high with levels between 150 to 199 mg/dL, high TG between 200 to 499 mg/dL, and very high TG as levels ≥ 500 mg/dL.[48] The 2012 guidelines on the evaluation and treatment of hypertriglyceridemia by the Endocrine Society (ES) state that severe and very severe hypertriglyceridemia increase the risk for pancreatitis, whereas mild or moderate hypertriglyceridemia may be a risk factor for CVD.[49] To take into account the risk for pancreatitis, the ES defines mild hypertriglyceridemia as TG levels between 150 to 199 mg/dL, moderate hypertriglyceridemia as TG levels between 200 to 999 mg/dL, severe hypertriglyceridemia as TG levels between 1,000 to 1,999 mg/dL, and very severe hypertriglyceridemia as TG levels ≥ 2,000 mg/dL. A high TG level is a component of metabolic syndrome, which is associated with risk for CVD. The ES recommends hypertriglyceridemia screening in adults as part of a lipid panel at least every 5 years and suggests that use of apo B or Lp(a) levels can be of value. Patients with primary hypertriglyceridemia should be evaluated for family history of dyslipidemia and CVD to assess genetic causes and future CVD risk. In addition to lifestyle changes, ES recommends drug therapy to reduce the risk of pancreatitis in patients with severe and very severe hypertriglyceridemia; a fibrate is considered first-line treatment. For patients with moderate to severe hypertriglyceridemia, fibrates, niacin, or omega-3 fatty acids alone or in combination with statins may be considered. Statins should not be used alone for severe or very severe hypertriglyceridemia; however, statins may be useful for the treatment of moderate hypertriglyceridemia to modify CVD risk. Recommended treatment goals for patients with moderate hypertriglyceridemia are non-HDL-C < 130 mg/dL in patients with CHD or a CHD Risk Equivalent (10-year risk for CHD > 20%), non-HDL-C < 160 mg/dL in patients with at least 2 risk factors, and non-HDL-C < 190 mg/dL in those with 0 to 1 risk factor.[50]

The Fredrickson classification was adopted by the World Health Organization (WHO) and categorized dyslipidemias by patterns of elevation in lipids and lipoproteins.[51] Type I (familial hyperchylomicronemia) is characterized by elevated chylomicrons and TGs; type IIa (familial hypercholesterolemia) by elevated LDL-C and total cholesterol; type IIb (familial combined hyperlipoproteinemia) by elevated LDL-C, very low density lipoprotein cholesterol (VLDL-C), TGs, and total cholesterol; type III (dysbetalipoproteinemia) by elevated VLDL, chylomicron remnants, TGs, and total cholesterol; type IV (primary hypertriglyceridemia) by elevated VLDL and TGs; and type V (mixed hypertriglyceridemia) by elevated chylomicrons, VLDL, TGs, and total cholesterol. The Fredrickson classification does not directly account for HDL, and it does not distinguish among the different genes that may play a role in dyslipidemia.

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Studies to date have not demonstrated an overall benefit of fibrates for reduction of CV events or total mortality; although *post-hoc* subgroup analyses have reported a decrease in composite CV events with the use of fibrates in patients with moderate hypertriglyceridemia.[52] Notably, the REDUCE-IT trial revealed that icosapent ethyl reduces CV event risk by 25%.[53]

In 2017, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) published guidelines for the management of dyslipidemia and prevention of cardiovascular disease.[54] In general, adults ≥ 20 years of age should be assessed annually for dyslipidemia; more frequent monitoring should be performed based on individual clinical circumstances. Lipid screening and management in the pediatric population is also addressed. AACE/ACE recommends screening children who are at risk for familial hypercholesterolemia (FH), defined as family history of either premature ASCVD or elevated cholesterol levels consistent with FH. At risk children for FH should be assessed at ages > 3 years, again between ages 9 to 11 years, and again at age 18 years. Adolescents > 16 years of age with ASCVD risk factors should be evaluated every 5 years. AACE/ACE support the use of apo B in evaluating lipids and recommends an optimal apo B < 90 mg/dL for patients at risk of CAD, while patients with established CAD or diabetes who have ≥ 1 additional risk factor have an apo B < 80 mg/dL. The 2017 AACE guidance recommends pharmacotherapy for children and adolescents > 10 years who do not respond sufficiently to lifestyle modification and for those with either LDL-C ≥ 190 mg/dL or LDL-C ≥ 160 mg/dL and the presence of ≥ 2 CV risk factors, a family history of premature CAD, or those who are obese, overweight, or insulin resistant. The 2017 guidelines also address the unique challenges associated with atherosclerosis and heart disease in women. AACE/ACE recommends the following pharmacotherapy for all women at high risk: lipid-lowering pharmacotherapy (preferably with a statin) regardless of LDL-C level and niacin or fibrate therapy in the presence of low HDL-C or elevated non-HDL-C; for all women at intermediate risk they recommend lipid-lowering pharmacotherapy (preferably with a statin) in the presence of an LDL-C > 130 mg/dL, as well as niacin or fibrate therapy in the presence of low HDL-C or elevated non-HDL-C after LDL-C goal is reached. In 2020, the AACE and ACE published a consensus statement algorithm for the management of dyslipidemia and prevention of CV disease to complement the 2017 AACE/ACE Guidelines for Management of Dyslipidemia and Prevention of CV Disease and incorporates new data not available at the time of the 2017 guidelines.[55] AACE/ACE maintains statins as primary therapy and their 2020 algorithm recommends treatment intensification with the addition of other LDL-C lowering agents (e.g., PCSK9 inhibitors, ezetimibe, colesevelam, or bempedoic acid) as needed to reach treatment goals. Although CV outcome trials (CVOTs) with colesevelam or bempedoic acid (BA) are not published, outcome trials with statins and ezetimibe or a PCSK9 inhibitor suggest further reduction in LDL-C though any combination of drugs would provide ASCVD benefits. Thereby, the 2020 AACE/ACE algorithm advocates for progression of therapy intensity in order to reach LDL-C targets. The 2019 approval of icosapent ethyl marked the first FDA approval for a medication that lowers TGs and reduces ASCVD. As the REDUCE IT trial used for approval showed a TG decrease of only 18%, the 2020 AACE/ACE algorithm states the CV outcome benefit does not appear to be related to the reduction in TGs. For patients with hypertriglyceridemia who do not have established ASCVD or diabetes with ≥ 2 risk factors and are not at the TG goal of < 150 mg/dL with statin therapy, then a fibrate, omega-3 fatty acid, or niacin can be considered. In order to decrease the potential for acute pancreatitis, all patients with severe hypertriglyceridemia (> 500 mg/dL) should receive a fibrate, prescription-grade omega-3 fatty acid, and/or niacin. Niacin can be used to reduce TG and LDL-C and to increase HDL-C, although its principal role is as adjunctive therapy to reduce TG.[56] Omega-3 fish oil (2 g to 4 g) can be used as adjunct to fibrates or niacin if necessary to achieve satisfactory triglyceride lowering in patients with

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TG > 500 mg/dL. AACE recommends bile acid sequestrants to reduce LDL-C and apo B and to modestly increase HDL-C, but these agents may increase triglycerides and, therefore, should be used with caution in patients with TG increases. Ezetimibe, is effective as monotherapy to decrease LDL-C and apo B, particularly in statin-intolerant patients. In addition, combination therapy with statins can be used. A new CV risk category of "extreme risk" was also included in the 2017. Treatment goals based on ASCVD risk are as follows.

AACE/ACE Treatment Goals[57]

Risk category	Risk factors/10-year risk	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)	TG (mg/dL)
Extreme risk	▪ Progressive ASCVD including unstable angina in patients after achieving an LDL-C <70 mg/dL ▪ Established clinical cardiovascular disease in patients with DM, CKD ≥ 3, or HeFH ▪ History of premature ASCVD (< 55 years male, < 65 years female)	< 55	< 80	< 70	< 150
Very high risk	▪ Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% ▪ Diabetes with ≥ 1 risk factor(s) ▪ CKD ≥ 3 with albuminuria ▪ HeFH	< 70	< 100	< 80	< 150
High risk	▪ ≥ 2 risk factors and 10-year risk 10% to 20% ▪ Diabetes or CKD ≥ 3 with no other risk factors	< 100	< 130	< 90	< 150
Moderate risk	▪ < 2 risk factors and 10-year risk < 10%	< 100	< 130	< 90	< 150
Low risk	▪ No risk factors	< 130	< 160	not recommended	< 150

In 2017, the American College of Cardiology (ACC) updated its 2016 consensus decision pathway for the use of non-statin LDL-C lowering drugs in patients with clinical ASCVD.[58] Factors that may help identify ASCVD patients who are at higher risk for recurrent events include the following: age ≥ 65 years, previous MI or nonhemorrhagic stroke, daily cigarette smoking, residual coronary artery disease (CAD) with ≥ 40% stenosis in ≥ 2 large vessels, HDL-C < 40 mg/dL for men and < 50 mg/dL for women, hs-CRP > 2 mg/L, or metabolic syndrome. For adults who are taking statins for secondary prevention and have an LDL-C level of 70 to 189 mg/dL, the threshold for a net risk-reduction benefit remains to be an LDL-C reduction ≥ 50%, but targets of LDL-C < 70 mg/dL or a non-HDL-C < 100 mg/dL may be considered for all patients, regardless of comorbidity. For patients who are in this LDL-C range with comorbidities, ezetimibe or a PCSK9 inhibitor may be considered. While ezetimibe may be favored in patient who require additional LDL-C reduction < 25%; a PCSK9 inhibitor may be preferred in patients who require > 25% LDL-C reduction. In addition, ACC down-graded their recommendations on use of

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bile acid sequestrants, to use only as a secondary alternative in patients intolerant to ezetimibe. ACC also included clinical diagnostic criteria for heterozygous and homozygous familial hypercholesterolemia, with and without the use of genetic testing.

The National Lipid Association (NLA) published Parts 1 and 2 of their new recommendations for patient-centered management of dyslipidemia in 2015.[59,60] Atherosclerosis develops over decades often beginning in childhood. Targeted lipid screening should begin at 2 years of age if warranted by family history; universal screening is appropriate at ages 9 to 11 years and repeated at age 20 years. The NLA recommends using lipid levels in conjunction with other ASCVD risk factors to assess overall risk and also support the use of risk calculators, such as the ATP III Framingham Risk Score and the ACC/AHA Pooled Cohort Equations. The NLA considers non-HDL-C to be superior to LDL-C for predicting ASCVD event risk since non-HDL-C is better correlated with apo B, and is more closely associated with the total burden of atherogenic particles. Non-HDL-C measurements are used along with LDL-C as primary targets of therapy. Triglyceride level is associated with the VLDL-C level, therefore using non-HDL-C as a target also simplifies the management of patients with high triglycerides. Desirable targets in patients with low, moderate, and high risk of an ASCVD event are non-HDL-C < 130 mg/dL and LDL-C < 100 mg/dL; in patients considered to be at very high risk target measures are < 100 mg/dL and < 70 mg/dL, respectively. The NLA advises that the intensity of risk-reduction therapy should be based on the patient's absolute risk for an ASCVD event. The NLA recommends lifestyle therapies such as diet modification and moderate physical activity before initiating drug therapy for patients at low and moderate ASCVD event risk; however, in patients at high or very high risk, drug therapy may be prescribed from the start. Moderate to high intensity statin therapy is considered first-line drug therapy. Non-statin agents, such as ezetimibe, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid can be considered in patients with contraindications or intolerance to statins, or as an add-on to maximally tolerated statin therapy if cholesterol levels are still elevated with maximally tolerated statin doses. If very high triglycerides (≥ 500 mg/dL) exist, a triglyceride-lowering drug may be considered for first-line use to prevent pancreatitis. Response and adherence to therapy should be monitored every 4 to 12 months. The NLA recommends review of both cholesterol goals and adherence to therapy with patients at each visit to identify barriers or side effects; an interdisciplinary team approach should be used whenever possible. Statins remain the drug therapy of choice for those with increased cardiovascular risk conditions, including HIV/AIDS and rheumatoid arthritis, and those at risk based on ethnicity or race, such as Hispanics, African Americans, and South Asians. The NLA outlines special considerations to take into account when treating these specific patient populations. In 2017, NLA published an update to the 2015 Part 2 to include new evidence on the use of PCSK9 inhibitors in adults.[61] They recommend consideration of PCSK9 inhibitors in patients with ASCVD (stable or progressive) or LDL-C ≥ 190 mg/dL (including polygenic hypercholesterolemia, HeFH, HoFH) based on factors such as age, other ASCVD risk factors, use of on maximally-tolerated statin therapy ± ezetimibe, and on-treatment LDL-C or non–HDL-C levels. Subsequently, in 2019, the NLA published a statement on the enhanced value of the PCSK9 inhibitors based on CV outcomes data as well as reductions in list prices.[62] Since risk reduction is directly proportional to absolute LDL-C, patients with higher starting ASCVD risk and higher LDL-C levels generally achieved greater reduction in major vascular events when treated with anti-hyperlipidemic pharmacotherapy. Based, at least in part, on ASCVD risk phenotype and LDL-C thresholds, the NLA determined that PSCK9 inhibitors will provide reasonable value in the following 3 groups of patients on maximally tolerated statin therapy: (1) extremely high-risk (≥ 40% 10-year ASCVD risk) patients with LDL-C ≥ 70 mg/dL, including patients with extensive or active ASCVD burden and those with less extensive ASCVD plus extremely high-risk

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cardiometabolic risk factors; (2) very high-risk (≥ 30% to 39% 10-year ASCVD risk) patients with LDL-C ≥ 100 mg/dL; and (3) high-risk (< 30% 10-year ASCVD risk) patients with LDL-C ≥ 130 mg/dL, including patients with HeFH or severe hypercholesterolemia ≥ 220 mg/dL. It is generally advised to add ezetimibe to statin therapy before adding a PCSK9 inhibitor; however, the NLA states that adding a PCSK9 inhibitor directly to a statin may be more efficacious for select patients at very high and extremely high ASCVD risk, particularly if their LDL-C is at a lower level.

In March 2017, the AHA published a Science Advisory on the use of omega-3 polyunsaturated fatty acid (PUFA) supplementation for the prevention of clinical CVD.[63] They state that PUFA supplementation is reasonable in patients with coronary heart disease (CHD) to reduce CHD-related mortality. Benefit of reduced hospitalization and improved survival have been shown in clinical studies in patients with HF and reduced left ventricular function. There are no published data to support its use in patients with diabetes, pre-diabetes, or a history of stroke, or for primary prevention of stroke or atrial fibrillation. In August 2019, the AHA released a Science Advisory on omega-3 fatty acid use for the management of hypertriglyceridemia.[64] They instruct for patients with very high TG (≥ 500 mg/dL), treatment with eicosatetraenoic acid (EPA) plus docosahexaenoic acid (DHA) at a dose of 4 grams/day reduces TG by ≥ 30% and increases LDL-C; however, EPA-only agents did not raise LDL-C in this population. For hypertriglyceridemia (TG, 200 to 499 mg/dL), EPA+DHA and EPA-only appear roughly comparable for TG lowering, resulting in a 20% to 30% reduction and no increase in LDL-C. The AHA concludes that prescription omega-3 fatty acid at doses of 4 grams/day are safe and effective for reducing TG either as monotherapy or as an adjunct to a statin.

Familial hypercholesterolemia (FH) is a genetic disorder that leads to accumulation of LDL-C particles in plasma and premature CV disease.[65,66] The more severe form, homozygous familial hypercholesterolemia (HoFH), is rare, occurring in about 1 out of a million people in the US. In HoFH, LDL receptor activity is nearly absent and LDL-C levels commonly range between 400 mg/dL to 1,000 mg/dL. Severe and widespread atherosclerosis affects all major arteries and children are at risk for early coronary events and valve abnormalities, particularly aortic stenosis. Historically, treating patients with HoFH has been very difficult since it is resistant to diet modifications and most medications indicated for lowering cholesterol. The less serious, heterozygous familial hypercholesterolemia (HeFH), occurs in 1 in 200 to 250 persons in industrialized countries. CAD symptoms begin to manifest in the fourth and fifth decades of life, in men and women, respectively. Additional risk factors (e.g., genetic, metabolic, and environmental) can lead to variations in the clinical manifestations and severity of atherosclerotic disease of HeFH. Accumulation of cholesterol in nonvascular tissue (cornea, skin, tendons, and joints) also commonly occurs in children with HoFH, and in adults with HeFH.

In the 2015 Agenda for Familial Hypercholesterolemia, the AHA advises that FH treatment be based on LDL-C levels, not genetic abnormality or other clinical features with an initial goal in LDL-C reduction by at least 50%.[67] This can be followed by achieving an LDL-C < 100 mg/dL (absence of CAD or other major risk factors) or < 70 mg/dL (presence of CAD or other major risk factors). The maximal LDL-C reduction that can be tolerated with therapy is a practical target, particularly for higher-risk patients. Therapeutic targets for apo B and non-HDL-C have not been defined for FH. Initial drug monotherapy for those with FH includes high-intensity statin therapy (rosuvastatin or atorvastatin). If LDL-C goal is not met within 3 months of adherent therapy, ezetimibe should be added. If after another 3 months, LDL-C goal is still not met, the addition of a PCSK9 inhibitor, a bile acid sequestrant (colesevelam), or prescription strength niacin should be considered. In most patients with HoFH, high dose statin therapy provides

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only modest reductions in LDL-C of 10% to 25%; however, CV and all-cause mortality has shown to occur even with modest LDL-C reduction. The addition of ezetimibe to statin therapy may provide an additional 10% to 15% LDL-C reduction. Other agents such as bile acid sequestrants, niacin, and fibrates result in only modest LDL-C-reducing effects in patients with HoFH. Four-drug combination therapy with the addition of lomitapide can be considered in patients with HoFH if needed. Dietary and lifestyle modifications should also be an aspect of FH treatment.

The 2020 type 2 diabetes management algorithm by the AACE/ACE advises early and intensive management of dyslipidemia in patients with type 2 diabetes mellitus (T2DM) to decrease the risk for ASCVD.[68] Some patients may achieve lipid goals with lifestyle therapy, but most will require pharmacotherapy to reduce CV risk. Moderate- to high-intensity statin therapy is recommended as first-line lipid-lowering drug therapy unless contraindicated. PCSK9 inhibitors provides a more aggressive lipid-lowering therapy and can provide further reduction of residual ASCVD risk in patients with clinical ASCVD and diabetes.

In 2020, the American College of Cardiology (ACC) published an expert consensus decision pathway focused on novel therapies for CV risk reduction in patients with type 2 diabetes.[69] For patients ≥ 18 years with type 2 diabetes and ≥ 1 of the following ASCVD, heart failure (HF), diabetic kidney disease (DKD), or at high risk for ASCVD, it is recommended to concurrently optimize guideline-directed medical therapy for prevention (lifestyle, blood pressure, lipids, glucose, and antiplatelets) and initiate a sodium-glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 receptor agonist (GLP-1RA) with proven CV benefit, depending on patient-specific factors, comorbid conditions, and patient-clinician preferences and priorities.

In their 2020 Standards of Medical Care in Diabetes, the American Diabetes Association (ADA) states that it is reasonable to obtain a lipid profile at initiation of statins or other lipid-lowering therapy, 4 to 12 weeks after initiation or a change in dose, and annually thereafter in patients on lipid-lowering therapy.[70] The ADA recommends moderate- or high-intensity statin therapy in patients with diabetes based on patient age and presence of ASCVD or 10-year ASCVD risk factors. For diabetic patients with a 10-year ASCVD risk of ≥ 20%, addition of ezetimibe to maximally tolerated statin therapy may be considered for reducing LDL-C by ≥ 50%. For diabetic patients with very high risk ASCVD and LDL-C ≥ 70 mg/dL on a maximally tolerated statin dose, additional LDL-lowering therapy, such as ezetimibe or PCSK9 inhibitor, can be considered. The ADA recommends against the addition of niacin or a fibrate to statin therapy in diabetic patients due to lack of additional benefit and advises of the increased risk of abnormal transaminase levels, myositis, and rhabdomyolysis with combination therapy with a statin and fibrate. Furthermore, the combination of a statin plus niacin may increase the risk for stroke. Based on data from the REDUCE-IT and DECLARE-TIMI 58 trials, the ADA now states that icosapent ethyl can be considered for reduction of CV risk in select patients (on a statin with controlled LDL-C but increased TGs) with diabetes and ASCVD or other cardiac risk factors for primary and secondary prevention.

The American Academy of Pediatrics (AAP) endorsed guidelines by the NHLBI on CV health and risk reduction in children and adolescents that outlines age appropriate lipid screening in the pediatric population.[71] NHLBI recommends a fasting lipid profile in children aged 1 to 4 years, only if the child is FH positive, the child has a parent with dyslipidemia, or if the child has any other risk factors or high-risk conditions. All children should be screened for high cholesterol at least once between the ages of 9 and 11 years, and again between ages 17 and 21 years. It is anticipated that a universal screening will more accurately identify children who are at high risk for CV disease. The guideline also identifies age-

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specific strategies to reduce risk factors and manage CV disease in children and adolescents. Most children with high cholesterol should be treated with lifestyle modifications including diet and physical activity. Less than 1% of children, primarily those with genetic dyslipidemias, may qualify for cholesterol-lowering medications. In addition to lifestyle interventions, the use of lipid-lowering medications is recommended, in general, in ages ≥ 10 years if LDL-C is ≥ 190 mg/dL, ≥ 160 mg/dL with family history of early heart disease or 1 high- or 2 moderate-level additional risk factors, or > 100 mg/dL if diabetes mellitus is present. The initial LDL-C goal is < 160 mg/dL, but LDL-C as low as 130 or even 110 mg/dL is warranted if strong CVD family history is present. Drug therapy may be considered for children ages 8 and 9 years with LDL-C persistently > 190 mg/dL combined with a strong family history of early CVD or additional risk factors.

In contrast, the US Preventive Services Task Force (USPSTF) issued a final recommendation in July 2016 regarding lipid screening in children and adolescents and states that the evidence is insufficient to weigh the risk and benefit of screening for lipid disorders in patients < 20 years.[72]

Data obtained during clinical trials have demonstrated that statin efficacy does not increase proportionally with dose.[73,74] This is referred to as the rule of 6%; doubling a statin dose results in approximately an additional 6% decrease in LDL-C, although the actual percentage may vary slightly among individuals. Thus, if it is known that a patient is unlikely to meet a goal LDL-C based on this limitation of statins, the addition of a PCSK9 inhibitor or bempedoic acid (not yet addressed in guidelines) may be appropriate in select patients.

A trial evaluating the effects of bempedoic acid on incidence of major adverse cardiovascular events in statin intolerant patients is ongoing; results are expected in second half of 2022.

PHARMACOLOGY[75,76,77,78,79,80,81,82,83]

ACL Inhibitors

Adenosine Triphosphate-Citrate Lyase (ACL) is an enzyme found upstream from 3-hydroxy-3-methyl-glutaryl-coezyme A (HMG-CoA) reductase that catalyzes the formation of acetyl-CoA and oxaloacetate from citrate.[84] Acetyl-CoA generated from this reaction then undergoes enzymatic conversion by HMG-CoA synthase and HMG-CoA reductase to form cholesterol. Bempedoic acid (Nexletol), a prodrug that is activated in the liver, lowers cholesterol synthesis and low-density lipoprotein cholesterol (LDL-C) by inhibiting ACL and upregulating LDL receptors. Bempedoic acid is also found in bempedoic acid/ezetimibe (Nexlizet), a combination ACL and cholesterol absorption inhibitor.

Apolipoprotein B (apo B) Synthesis Inhibitors

Apolipoprotein B (apo-B) is a structural protein of very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL).[85] Microsomal triglyceride transfer protein (MTP) transfers triglycerides onto apo B during the production of VLDL, a precursor to LDL.[86]

Lomitapide (Juxtapid) directly binds and inhibits MTP, preventing the synthesis of apo-B-containing proteins in enterocytes and hepatocytes. This results in decreased synthesis of VLDL and, thereby, reduced plasma LDL-C levels. MTP inhibitors are not liver-specific and thus block the secretion of both intestinal and hepatic lipoproteins. This lack of inhibition specificity can lead to fat malabsorption in some patients.

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Bile Acid Sequestrants

During normal digestion, bile acids are secreted into the intestines. Bile acids emulsify the dietary fat thus facilitating absorption. A major portion of the bile acids is absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation. The bile acid sequestrants, cholestyramine, colestipol (Colestid), and colesevelam (Welchol), bind bile acids in the intestine to form an insoluble complex which is excreted in the feces, thereby interrupting enterohepatic circulation. As the bile acid pool becomes depleted, the hepatic enzyme cholesterol, 7 α-hydroxylase, is upregulated. Upregulation of 7 α-hydroxylase increases the conversion of cholesterol to bile acids with a resulting increase in demand for cholesterol in the liver cells. The hepatic demand for cholesterol causes a dual effect of 1) increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase and 2) increasing the number of hepatic LDL-C receptors. These compensatory mechanisms increase clearance of LDL-C from the blood, resulting in decreased serum LDL-C levels. In patients with partial biliary obstruction, the reduction of serum bile acid levels reduces excess bile acids deposited in the dermal tissue with resultant decrease in pruritus.

Bile acid sequestrants can reduce LDL-C levels by 12% to 30% and may have a small effect on HDL-C. Reports of impact vary, but bile acid sequestrants may increase TGs. The complementary mechanisms of action of bile acid sequestrants and statins makes them well suited for combination therapy. Combinations of bile acid sequestrants with non-statin lipotropics may be useful in patients who are intolerant to statin therapy.[87] Cholestyramine has been shown to reduce the number of CV events, but colestipol or colesevelam do not have CV clinical outcomes data.

The mechanism of action of colesevelam in glycemic control is unknown.

Cholesterol Absorption Inhibitors

Ezetimibe (Zetia) inhibits cholesterol absorption along the brush border of the small intestine. This leads to a decrease in the delivery of intestinal cholesterol to the liver, reduction of hepatic cholesterol stores, and an increase in cholesterol clearance from the blood. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe inhibits absorption of both dietary cholesterol and cholesterol in bile. Ultimately, ezetimibe reduces total cholesterol (total-C), LDL-C, TG, and apo B, and increases HDL-C in patients with hypercholesterolemia. When ezetimibe is administered with a statin, further improvements on the lipid profile occur.

Addition of ezetimibe to stable bile acid sequestrant therapy has been shown to reduce total-C by 18%, TG by 14%, and LDL-C by 19% after 3 to 4 months. The combination had no effect on HDL-C and was well tolerated.[88]

Fibric Acids

The effects of the fibric acids, fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide), fenofibric acid (Fibricor, Trilipix; the active metabolite of fenofibrate), and gemfibrozil (Lopid), have been explained by the activation of peroxisome proliferator activated receptor alpha (PPARα). Through this mechanism, the fibric acids increase lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase. Fibric acids reduce production of apoproteins C-III, an inhibitor of lipoprotein lipase activity. The resulting fall in TG produces an alteration in the size and composition of LDL-C from small, dense particles, which are thought to be atherogenic due to their susceptibility to oxidation, to large

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buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I and A-II, as well as HDL-C. Fenofibrate also reduces serum uric acid levels by increasing urinary excretion of uric acid. Each fenofibric acid (Trilipix) delayed-release capsule contains the choline salt of fenofibric acid, which is converted to fenofibric acid in the gastrointestinal tract.[89] Fenofibric acid is thought to be more readily absorbed and less affected by food than fenofibrate.

Gemfibrozil has been shown to reduce the risk of CHD in patients with high TG and low HDL-C.[90,91,92,93] This effect is most significant in patients with diabetes or metabolic syndrome.[94] ACC/AHA advises that gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. Gemfibrozil use with simvastatin is contraindicated. Fenofibrate, however, does not interfere with statin metabolism and may be less likely to increase the risk for myopathy in patients treated with moderate doses of statins.[95,96]

Fenofibrate did not demonstrate in patients with type 2 diabetes a statistically significant reduction in the risk of first nonfatal MI and CHD death in the FIELD study; although nonfatal MI was significantly reduced.[97,98] In the lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, the combination of fenofibrate and simvastatin did not significantly reduce the rate of fatal CV events, nonfatal MI, or nonfatal stroke, compared with simvastatin monotherapy (HR 0.92, 95% CI 0.79 to 1.08; p=0.32), suggesting against the routine use of combination therapy with fenofibrate and simvastatin to reduce CV risk in the majority of high-risk patients with type 2 diabetes.[99] Based on results from the ACCORD Lipid trial and other clinical trials, in November 2011, the FDA informed the public that fenofibric acid (Trilipix) may not lower a patient's risk of having a MI or stroke and required the manufacturer of Trilipix to conduct a clinical trial to evaluate the CV effects of Trilipix in patients at high risk for CV disease who were already taking statins.[100] In addition, a subgroup analysis of ACCORD showed there was an increase in the risk for major adverse cardiac events in women, relative to men, receiving the combination therapy versus simvastatin alone.[101] The clinical significance of this subgroup finding is unclear, as this finding was not observed in a separate large randomized controlled clinical trial of fenofibrate versus placebo. Data to support the routine use of non-statin drugs in combination with statin therapy to reduce further ASCVD events are lacking; however, non-statin therapy may be considered as adjunct to statin therapy when maximum intensity statin therapy does not lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C.[102] In April 2015, the FDA removed the indication for fenofibric acid (Trilipix) as an adjunct to diet in combination with a statin to reduce triglycerides and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.[103]

Niacin (nicotinic acid)

Niacin (nicotinic acid) inhibits lipolysis in adipocytes and possibly inhibits hepatic TG production resulting in a reduction in the synthesis of VLDL that is available for conversion to LDL-C. It may involve several actions, including partial inhibition of the release of free fatty acids from adipose tissue and increased lipoprotein lipase activity. Niacin also increases HDL-C by reducing the hepatic uptake of HDL-C. Nicotinic acid increases HDL-C levels by 15% to 35% and has shown to decrease total cholesterol by 10% and triglycerides by 27%.[104,105] Immediate-release niacin (Niacor) is available with a prescription. It is also available without a prescription. Due to intolerance, patients often need to take aspirin prior to each dose to reduce the vasodilation and flushing associated with niacin immediate-

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release. To increase tolerance, a film-coated, niacin extended-release (Niaspan) has been developed and is available with a prescription.

Combination therapy with niacin and statins yields a significant reduction in LDL-C and increase in HDL-C.[106] Niacin has been shown to reduce the risk of CHD as monotherapy and in combination with statins.[107,108,109] It also led to regression of carotid atherosclerosis when given with statins in a small study.[110,111] Niacin caused regression of coronary lesions and reduced CV events in another small study when given in combination with cholestyramine and gemfibrozil.[112]

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) included 3,414 patients with established CVD and atherogenic dyslipidemia. All patients received simvastatin, with or without ezetimibe, at a dose sufficient to maintain LDL-C at 40 to 80 mg/dL. Patients were randomized to niacin extended-release (ER) or matching placebo.[113] Although niacin ER was effective at raising HDL-C and lowering triglycerides, the trial was halted early due to the lack of incremental benefit on CV risk reduction (including MI and stroke) in the niacin ER plus simvastatin arm versus simvastatin alone (p=0.8).[114,115] In addition, a small, unexplained, increase in the rate of ischemic stroke was observed in the simvastatin plus niacin ER arm compared to simvastatin alone (29 patients versus 18 patients, respectively; p=0.11). Nine of the ischemic strokes in the simvastatin plus niacin ER group occurred in participants who had stopped taking niacin for at least 2 months and up to 4 years before their stroke. Therefore, it is unclear whether niacin contributed to this imbalance in ischemic stroke. The authors note many study limitations, such as that the findings may not be generalizable to all patients with coronary disease or all patients with low HDL-C levels. It remains unclear whether other populations may benefit from such treatment; it is unclear if in the 94% of patients who were taking statins at study entry whether or not they had more stable plaques at baseline which were less likely to rupture, and therefore, had a lower risk of subsequent CV events. The low percentage of women enrolled (15%), the low rate of ethnic minorities (8%), and the 36-month follow-up period may not have been adequate to show a clinical treatment effect of niacin. The AIM-HIGH trial was funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health (NIH) with additional support from Abbott Laboratories. The FDA plans to conduct a review of AIM-HIGH.[116] In April 2016, the FDA removed the indication for niacin ER (Niaspan) in combination with simvastatin or lovastatin for the treatment of primary hyperlipidemia and mixed dyslipidemia when treatment with Niaspan, simvastatin, or lovastatin monotherapy is considered inadequate.[117]

Omega-3 Fatty Acids

Omega-3-acid ethyl esters (Lovaza) is a combination of ethyl esters – 465 mg of eicosapentaenoic acid (EPA) and 375 mg of docosahexaenoic acid (DHA). These 2 fatty acids are found in fish oil and have been shown to be a contributing factor in the beneficial effects of frequent consumption of oily fish.[118] The mechanism of action of omega-3-acid ethyl esters is not completely understood. It is thought that the omega-3-acid ethyl esters may reduce the synthesis of TG by the liver. Beneficial effects on lipids by omega-3-acid ethyl esters include reduced TG and VLDL and increases in HDL-C. Elevations in LDL-C and non-HDL-C may also be observed. In trials done with omega-3-acid ethyl esters, the median percent change in LDL-C was an increase of 49.3% relative to placebo. EPA and DHA have also been shown to demonstrate anti-inflammatory and cardioprotective effects, including possible antiarrhythmic effects and changes in heart rate variability. Omega-3-acid ethyl esters 4 grams per day have been shown to reduce TG by up to 45% in adults with baseline TG ≥ 500 mg/dL.

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Icosapent ethyl (Vascepa) is an ethyl ester of EPA only. Icosapent ethyl 4 grams per day has been shown to reduce TG by up to 33.1% in adults with baseline TG ≥ 500 mg/dL while elevations of LDL-C have not been observed.[119]

The use of EPA alone does not affect LDL-C like the combination of EPA and DHA can, due to an increased conversion of VLDL to LDL. In the pivotal clinical trials, treatment with icosapent ethyl was not associated with elevations in LDL-C compared to placebo. The median reduction in triglycerides in omega-3-acid ethyl esters-treated patients from pivotal trials was 27% (33% relative to placebo).

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Alirocumab (Praluent) and evolocumab (Repatha) are human monoclonal antibodies that bind to PCSK9. PCSK9 binds to low density lipoprotein receptors (LDLR) at the surface of hepatocytes and, thereby, targets internalized LDLR for lysosomal degradation. By inhibiting the binding of PCSK9 to LDLR, these agents increase the number of LDLR available to clear LDL particles, thereby lowering LDL-C.

Significant reductions in LDL-C by approximately 40% to 60% ($p<0.0001$) have been reported for alirocumab compared with placebo. Similar reductions in non-HDL-C levels and apo B were also observed. In phase 3 clinical trials, patients treated with evolocumab experienced an average LDL-C reduction of approximately 30% to 70% ($p<0.0001$).

PHARMACOKINETICS[120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142]

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
ACL Inhibitors				
bempedoic acid (Nexletol)	unknown	21	ESP15228 (active metabolite); glucuronide conjugates	urine: 70 feces: 30
ACL Inhibitor/Cholesterol Absorption Inhibitor				
bempedoic acid/ ezetimibe (Nexlizet)	unknown 35-60	21 22	ESP15228 ezetimibe glucuronide	see individual components
Apolipoprotein B Synthesis Inhibitor				
lomitapide (Juxtapid)	7	39.7	major: M1 and M3 (CYP 3A4)	urine: 59.5 feces: 33.4
Bile Acid Sequestrants				
cholestyramine	not absorbed	--	--	feces
colesevelam (Welchol)	not absorbed	--		
colestipol (Colestid)	not absorbed	--		
Cholesterol Absorption Inhibitors				
ezetimibe (Zetia)	35-60	22	ezetimibe glucuronide	urine: 11 feces: 78

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Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
Fibric Acids				
fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide)[143]	unknown	16-23	fenofibric acid (active component); glucuronide conjugate	urine: 60 feces: 25
fenofibric acid (Fibricor)	unknown	20	glucuronide conjugate	urine
fenofibric acid (Trilipix)	81	20	glucuronide conjugate	urine
gemfibrozil (Lopid)	100	1.5	3 metabolites	urine: 70 feces: 6
Niacin				
niacin ER (Niaspan)	60-76	--	many metabolites	predominantly urine
niacin IR (Niacor)	88	0.3-0.75	nicotinuric acid	urine
Omega-3 Fatty Acids				
icosapent ethyl (Vascepa)	--	89	acetyl Coenzyme A	hepatic
omega-3-acid ethyl esters (Lovaza)	unknown	--	--	--
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors				
alirocumab (Praluent)	85	17-20 days	--	saturable binding to target (PCSK9) at low concentrations; non-saturable proteolytic pathway at higher concentrations
evolocumab (Repatha)	72	11-17 days	--	

Fenofibrate micronized 67 mg capsule has been shown to provide similar therapeutic effects to fenofibrate "non-micronized" 100 mg capsule.[144] All currently available fenofibrate products at the highest available dose produce similar plasma concentrations as the fenofibrate 200 mg capsules in single dose studies. Lipofen 150 mg capsules have been shown to be equivalent to Tricor 160 mg tablets under low-fat and high-fat fed conditions. Fenoglide 120 mg tablets have been shown to be equivalent to fenofibrate 130 mg capsules under high-fat conditions. Trilipix 135 mg capsules are equivalent to micronized fenofibrate 200 mg capsules administered under fed conditions. Fibricor 105 mg tablets are equivalent to fenofibrate tablets (Tricor) 145 mg under fasted conditions.

CONTRAINDICATIONS/WARNINGS[145,146,147,148,149,150,151,152,153,154,155,156,157,158159,160,161,162,163,164,165,166,167,168]

Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitor

There are no contraindications for use of bempedoic acid (Nexletol); however, the combination product, bempedoic acid/ezetimibe (Nexlizet) is contraindicated in patients with known hypersensitivity to ezetimibe. Products containing bempedoic acid may result in increased blood uric acid levels due to the inhibition of renal tubular organic anion transporter 2 (OAT2). In clinical trials, patients treated with bempedoic acid experienced increased uric acid levels as early as 4 weeks after starting therapy with levels remaining elevated throughout treatment. An increased risk of the

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development of gout was reported in patients both with and without a prior history of gout, with higher risk in patients with a previous history. Patients experiencing symptoms of hyperuricemia should contact their healthcare provider and if needed, should have their serum uric acid level assessed. Treatment with urate-lowering medications may be necessary in some patients.

An increased risk of tendon rupture or injury has also been associated with products containing bempedoic acid. In clinical trials, tendon rupture or injury affecting the rotator cuff, Achilles tendon, and biceps tendon was reported within weeks to months after initiating bempedoic acid (0.5% versus 0 of placebo patients). Patients with previous tendon disorders, renal failure, > 60 years of age, and those receiving fluoroquinolone or corticosteroid medications may be at an increased risk for tendon rupture. Patients who have a history of tendon disorders or rupture should be considered for appropriate therapeutic alternatives. Patients experiencing tendon rupture should discontinue any product containing bempedoic acid immediately. Patients should contact their healthcare provider and rest should they experience any signs or symptoms of tendinitis or tendon rupture.

Apolipoprotein B (apo B) Synthesis Inhibitor

Lomitapide (Juxtapid) is contraindicated in patients with moderate or severe hepatic impairment (Child Pugh category B or C), or active liver disease, including unexplained persistent elevations of serum transaminases. Lomitapide carries a boxed warning due to the risk of hepatotoxicity resulting from increases in transaminases and hepatic steatosis. It can increase hepatic fat, with or without concomitant increases in transaminases. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be measured each month during the first year of lomitapide therapy and every 3 months thereafter.

Lomitapide is contraindicated in patients who are pregnant. It also carries a warning regarding embryo-fetal toxicity; females of reproductive potential should use effective contraception during and for 2 weeks following the last dose. Concomitant use of lomitapide with strong or moderate CYP3A4 inhibitors is also contraindicated.

Caution should be used when lomitapide is taken with other medications that are known to be hepatotoxic (e.g., isotretinoin, amiodarone, high doses of acetaminophen [> 4 g/day for ≥ 3 days], methotrexate, tetracyclines, tamoxifen). Alcohol may also increase levels of hepatic fat; therefore, patients taking lomitapide should not consume > 1 alcoholic beverage each day.

Due to lomitapide's mechanism of action in the small intestine, the absorption of fat-soluble nutrients may be reduced. Patients taking lomitapide should receive daily supplements containing 400 IU vitamin E, 200 mg linoleic acid, 210 mg alpha-linolenic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA). Patients with chronic bowel or pancreatic disease may be at increased risk for deficiencies in these nutrients.

Bile Acid Sequestrants

Bile acid sequestrants, cholestyramine, colestipol (Colestid), and colesevelam (Welchol), can raise triglyceride levels and are contraindicated in patients with very high triglyceride levels (> 500 mg/dL).[169] A lipid panel, including triglycerides, should be assessed prior to initiating colesevelam therapy as well as periodically thereafter. Patients with triglycerides levels > 300 mg/dL may experience higher triglyceride level increases when receiving colesevelam therapy and may require more frequent triglyceride monitoring. Colesevelam is also contraindicated in patients with bowel obstruction and in patients with hypertriglyceridemia-induced pancreatitis. Patients who experience

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triglyceride levels > 500 mg/dL or symptoms of acute pancreatitis should discontinue colesevelam therapy and seek immediate medical attention. Cholestyramine is contraindicated in complete biliary obstruction.

Because of its constipating effects, colesevelam is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction; bowel obstruction has been reported post-marketing.

Phenylketonuric patients should be aware that colesevelam oral suspension contains 13.5 mg phenylalanine per 1.875 gram packet and 27 mg phenylalanine per 3.75 gram packet.

Cholesterol Absorption Inhibitors

The combination of ezetimibe (Zetia) and a statin is contraindicated in patients with acute liver disease or unexplained persistent elevations in serum transaminases.

Use of bempedoic acid/ezetimibe (Nexlizet) in patients with a known hypersensitivity to ezetimibe is contraindicated.

Fibric acids

Fenofibrate products (Antara, Fenoglide, Lipofen, Tricor, Triglide), fenofibric acid (Fibricor, Trilipix), and gemfibrozil (Lopid) are contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, or pre-existing gallbladder disease, or with known hypersensitivity to the product. Fenofibrate and fenofibric acid are also contraindicated in patients with unexplained persistent liver enzyme elevations. Concomitant use of gemfibrozil with agents containing dasabuvir, repaglinide, selexipag, or simvastatin is also contraindicated. Caution should be used when prescribing a statin and gemfibrozil together due to an increased risk of myositis and rhabdomyolysis.

The use of fibric acids is not recommended in nursing mothers, and it is considered a contraindication for use in Fibricor, Trilipix, and Fenoglide. Fenofibrates and fenofibric acid may cause venous thromboembolic disease. Regular periodic monitoring of liver function should be performed for the duration of fenofibrate therapy, and therapy discontinued if enzyme levels persist > 3 times the upper limit of normal (ULN).

Fenofibrates and gemfibrozil can lead to cholelithiasis; therefore, these therapies should be discontinued if gallstones are found.

Reports of dramatic decreases in HDL-C levels (2 mg/dL) have occurred post-marketing in patients on fenofibrate therapy. This can occur weeks to months after initiation of fenofibrate therapy. HDL-C levels returned to normal once fibrate therapy is discontinued. Clinical significance is unknown, but it is recommended that HDL-C levels be monitored within the first few months of starting fibrate therapy.

There have been postmarketing reports of anaphylaxis, angioedema, and severe cutaneous adverse drug reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and interstitial lung disease with fenofibrate. Fenofibrate should be discontinued and appropriate treatment administered if SCAR is suspected.

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Niacin (nicotinic acid)

Niacin ER (Niaspan) is contraindicated in patients with chronic liver disease, active peptic ulcer disease, or arterial bleeding. Caution should also be used when niacin ER is used in patients with unstable angina or in the acute phase of a MI, particularly when such patients are also receiving vasoactive drugs, such as nitrates, calcium channel blockers, or adrenergic blocking agents. Caution should be used with niacin in patients predisposed to gout. Monitor liver function tests in all patients during therapy at approximately 6-month intervals or when clinically indicated. If transaminase levels are > 3 x ULN, or clinical symptoms of hepatic dysfunction are present, niacin should be discontinued. Niacin treatment can increase fasting serum glucose levels. Frequent monitoring of blood glucose should be performed.

An increased risk for myopathy in Chinese patients taking simvastatin co-administered with lipid-modifying doses of niacin (≥ 1 g/day) has been reported.[170] Therefore, concurrent usage of simvastatin with niacin doses ≥ 1 g/day is not recommended. The cause of the increased risk of myopathy is unknown. It is also unknown whether the risk for myopathy with co-administration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian populations.

Omega-3 Fatty Acids

Omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) should be used with caution in patients with a known history of sensitivity or allergy to fish and/or shellfish. Patients experiencing allergic reactions should discontinue therapy and seek medical attention. In patients with hepatic impairment, monitor liver transaminases periodically during therapy. Omega-3-acid ethyl esters may increase levels of LDL-C; therefore, periodic LDL-C monitoring during therapy is recommended. Icosapent ethyl

A clinical study has reported a potential association between omega-3-acid ethyl esters and increased recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within 2 to 3 months after initiation of therapy. This occurred in patients that had no substantial structural heart disease, were taking no anti-arrhythmic therapy (rate control permitted) and were in normal sinus rhythm at baseline.

Icosapent ethyl has also been associated with an increased incidence of atrial fibrillation or flutter requiring hospitalization. Patients with a prior history of atrial fibrillation or flutter have shown a higher incidence of atrial fibrillation.

An association with icosapent ethyl and increased bleeding risk has been shown. Patients taking icosapent ethyl with concurrent antithrombotic medications (e.g., aspirin, clopidogrel, warfarin) were shown to have a higher incidence of bleeding.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Alirocumab (Praluent) and evolocumab (Repatha) are contraindicated in patients with known hypersensitivity to alirocumab or evolocumab, respectively. Hypersensitivity reactions, such as rash, urticaria, and angioedema have been reported with both medications; pruritus, vasculitis, and reactions requiring hospitalization have been reported with alirocumab. Discontinue if signs or symptoms of an allergic reaction occur.

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Risk Evaluation and Mitigation Strategy (REMS)

Due to the risk of hepatotoxicity, lomitapide (Juxtapid) is only available through a restricted program under the REMS.[171] The goal of the REMS is to educate prescribers regarding the risk of hepatotoxicity, the need to monitor patients during therapy, and to restrict access to therapy with these agents to patients with a clinical or laboratory diagnosis consistent with HoFH. Only certified providers and pharmacies may prescribe and dispense lomitapide. Providers must complete a REMS program prescriber enrollment form, complete a prescriber training module, and submit a REMS prescription authorization form for each new prescription.

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DRUG INTERACTIONS[172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195]

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
ACL Inhibitor						
bempedoic acid (Nexletol)	--	--	--	--	--	increased risk of myopathy (simvastatin or pravastatin)
ACL Inhibitor/Cholesterol Absorption Inhibitor						
bempedoic acid/ezetimibe (Nexlizet)	reduced bioavailability of ezetimibe	--	increased ezetimibe concentration with risk of cholelithiasis	--	--	increased risk of myopathy (simvastatin or pravastatin)
Apolipoprotein B Synthesis Inhibitor						
lomitapide (Juxtapid)	administration with bile acid sequestrants can reduce lomitapide absorption	slight increase in ezetimibe exposure	decrease in fenofibrate, micronized exposure	increase in nicotinic acid exposure	--	increased risk of myopathy
Bile Acid Sequestrants						
cholestyramine, colestipol (Colestid)	--	reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate or fenofibric acid	reduced absorption of niacin	--	--
colesevelam (Welchol)	--	reduced bioavailability of ezetimibe	reduced bioavailability of fenofibrate or fenofibric acid	--	--	--
Cholesterol Absorption Inhibitors						
ezetimibe (Zetia)	reduced bioavailability of ezetimibe	--	increased ezetimibe concentration with risk of cholelithiasis	--	--	--

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Drug Interactions (continued)

Drug	Bile Acid Sequestrants	Cholesterol Absorption Inhibitor	Fibric Acids	Niacin	Omega-3 Fatty Acids	Statins
Fibric Acids						
fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide)	reduced bioavailability of fenofibrate	increased ezetimibe concentration with risk of cholelithiasis	--	--	--	increased risk of myopathy and rhabdomyolysis
fenofibric acid (Fibricor, Trilipix)	reduced bioavailability of fenofibric acid	increased ezetimibe concentration	--	--	--	increased risk of myopathy and rhabdomyolysis
gemfibrozil (Lopid)	reduced bioavailability of gemfibrozil when given at exact same time as colestipol	increased ezetimibe concentration with risk of cholelithiasis	--	--	--	increased risk of myopathy and rhabdomyolysis
Niacin						
niacin ER (Niaspan)	administration with cholestyramine or colestipol reduces absorption of niacin	--	--	--	--	increased risk of myopathy
niacin IR (Niacor)	--	--	--	--	--	increased risk of myopathy
Omega-3 Fatty Acids						
icosapent ethyl (Vascepa)	--	--	--	--	--	--
omega-3-acid ethyl esters (Lovaza)	--	--	--	--	--	--
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors						
alirocumab (Praluent)	--	--	--	--	--	--
evolocumab (Repatha)	--	--	--	--	--	--

Other Drug Interactions

Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitor – bempedoic acid (Nexlizet)

Statins: Concomitant use of bempedoic acid with simvastatin or pravastatin may lead to an increased simvastatin or pravastatin concentration and increased risk of myopathy. Avoid concurrent use with simvastatin doses > 20 mg and pravastatin doses > 40 mg.

ACL Inhibitor/Cholesterol Absorption Inhibitor – bempedoic acid/ezetimibe (Nexlizet)

Cholestyramine: Concurrent use of bempedoic acid/ezetimibe and cholestyramine may decrease ezetimibe concentration. Bempedoic acid/ezetimibe should be administered ≥ 2 hours before or 4 hours after a bile acid sequestrant.

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Cyclosporine: Concomitant use of bempedoic acid/ezetimibe and cyclosporine increases ezetimibe and cyclosporine concentrations. Cyclosporine levels should be monitored with concurrent use.

Fibric Acids: Fenofibrate and ezetimibe may each increase the risk of cholelithiasis. Co-administration of bempedoic acid/ezetimibe and fibrates, other than fenofibrate, is not recommended. If cholelithiasis is suspected in a patient receiving bempedoic acid/ezetimibe and fenofibrate, assess gallbladder function and consider alternative lipid-lowering therapy.

Statins: Concomitant use of bempedoic acid/ezetimibe with simvastatin or pravastatin may lead to an increased simvastatin or pravastatin concentration and increased risk of myopathy. Avoid concurrent use with simvastatin doses > 20 mg and pravastatin doses > 40 mg.

Apolipoprotein B Synthesis Inhibitor – lomitapide (Juxtapid)

CYP3A4 inhibitors: Concomitant use of strong CYP3A4 inhibitors (boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, tipranavir/ritonavir), and moderate CYP3A4 inhibitors (ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, verapamil) with lomitapide can significantly increase lomitapide exposure and are contraindicated. Lomitapide dose should not exceed 30 mg daily when used with weak CYP3A4 inhibitors (alprazolam, amiodarone, amlodipine, atorvastatin, cimetidine, cyclosporine, fluoxetine, ginkgo, ranitidine, ticagrelor); maximum dose with concomitant use of oral contraceptive is 40 mg daily. In women taking oral contraceptives, if vomiting or diarrhea occurs while on lomitapide, hormone absorption may be reduced, and use of additional contraceptive methods is warranted.

P-glycoprotein Substrates (P-gp): Co-administration of lomitapide with P-gp substrates (e.g., aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, fexofenadine, saxagliptin, sitagliptin) may increase the absorption of the P-gp substrate. Dose reduction of the P-gp substrate should be considered when used concomitantly with lomitapide.

Statins: Lomitapide increases simvastatin exposure. Reduce simvastatin dose by 50% when initiating lomitapide. Simvastatin dose should not exceed 20 mg daily or 40 mg daily for patients who have been tolerant to simvastatin 80 mg daily for at least 1 year. Although not studied, since metabolizing enzymes are similar for lovastatin and simvastatin, lovastatin dose reduction should be considered with concomitant use of lomitapide.

Warfarin: Lomitapide increases plasma concentrations of warfarin. Monitor the international normalized ratio (INR) appropriately, particularly after lomitapide dosage change.

Bile Acid Sequestrants – cholestyramine, colestipol (Colestid), and colesevelam (Welchol)

Diltiazem, mycophenolate: The bile acid sequestrants reduce the absorption of diltiazem and mycophenolate, regardless of the time of administration of the interacting drugs relative to each other.[196,197] Concomitant use of mycophenolate with the bile acid sequestrants is not recommended.

Vitamins: Bile acid sequestrants may decrease the absorption of fat-soluble vitamins A, D, E, and K. Patients on oral vitamin supplementation should take their vitamins at least 4 hours prior to a bile acid sequestrant. Caution should be exercised when treating patients with a susceptibility to deficiencies of vitamin K (e.g., patients on warfarin, patients with malabsorption syndromes) or other fat-soluble vitamins. Chronic use of cholestyramine can result in a folate deficiency. Supplementation may be necessary.

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Warfarin: Cholestyramine can reduce serum levels of warfarin by interfering with its enterohepatic circulation; dosage adjustments may be necessary.[198]

Other drugs: Since cholestyramine and colestipol may bind other drugs given concurrently, it is recommended that patients take other drugs at least 1 hour before or 4 to 6 hours after cholestyramine (or as great an interval as possible) to avoid impeding their absorption.

Colesevelam reduces levels of cyclosporine, glimepiride, glipizide, glyburide, levothyroxine, olmesartan, and oral contraceptives containing ethinyl estradiol and norethindrone. These agents should be administered at least 4 hours prior to colesevelam. Colesevelam increases the exposure of extended-release metformin. Colesevelam may also interact with concomitant therapy with phenytoin, warfarin, or other narrow therapeutic index drugs. Colesevelam can increase triglycerides in combination with insulin or sulfonylureas.

Cholesterol Absorption Inhibitor – ezetimibe (Zetia)

Cyclosporine: Using cyclosporine and ezetimibe together may result in increased plasma levels of both drugs; the mechanism of this interaction is unknown.

Fibric Acids – fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide), fenofibric acid (Fibricor, Trilipix), and gemfibrozil

Colchicine: Myopathy, including rhabdomyolysis, has been reported with concurrent use of fenofibrate or gemfibrozil with colchicine. Use caution when prescribing both agents.

Cyclosporine: Concomitant use of cyclosporine and fenofibrate or fenofibric acid (Fibricor, Trilipix) may decrease renal function.

CYP2C8 and OATP1B1 substrates: Gemfibrozil inhibits CYP2C8 and OATP1B1 and may increase exposure to substrates of these enzymes (e.g., dabrafenib, enzalutamide, loperamide, montelukast, paclitaxel, pioglitazone); dosing reductions may be necessary for the substrates. Concomitant use with the OATP1B1 substrates repaglinide and simvastatin is contraindicated.

Oral hypoglycemics: The concurrent use of gemfibrozil with glyburide (Glynase®), pioglitazone (Actos®), or rosiglitazone (Avandia®) may result in enhanced hypoglycemic effect.[199,200,201,202] The use of gemfibrozil with repaglinide (Prandin®) is contraindicated due to a significant increase in serum concentrations of the oral hypoglycemic.[203]

Statins: The concomitant administration of gemfibrozil with simvastatin is contraindicated.

Warfarin: Concomitant administration of fibric acids and warfarin increases the INR and the risk of bleeding.

Niacin – niacin IR and ER (Niacor and Niaspan)

Statins: Combination therapy with Niaspan and lovastatin or simvastatin should not exceed doses of 2,000 mg Niaspan and 40 mg lovastatin or simvastatin daily.

Warfarin: Caution should be observed when niacin is administered concomitantly with anticoagulants. Niacin has been associated with small but statistically significant increases (mean 4%) in prothrombin time (PT). Monitor INR periodically.

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Omega-3-Fatty Acids – omega-3-acid-ethyl esters (Lovaza), icosapent ethyl (Vascepa)

Anticoagulants: Omega-3-acids may prolong bleeding time. Patients taking Lovaza or Vascepa and an anticoagulant and/or antiplatelet or other drug affecting coagulation should be monitored periodically for bleeding.

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors – alirocumab (Praluent), evolocumab (Repatha)

No relevant drug-drug interactions for alirocumab or evolocumab are listed in the prescribing information.

ADVERSE EFFECTS[204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226]

Drug	Abdominal Pain	Back pain	Headache	Abnormal LFTs	Constipation	Dyspepsia
Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitor						
bempedoic acid (Nexletol)	3.1 (2.2)	3.3 (2.2)	nr	2.1 (0.8)	nr	nr
ACL Inhibitor/Cholesterol Absorption Inhibitor						
bempedoic acid/ezetimibe (Nexlizet)	reported	reported	nr	reported	4.7 (0)	nr
Apolipoprotein B Synthesis Inhibitor						
lomitapide (Juxtapid)	34	14	10	21	21	38
Bile Acid Sequestrants						
cholestyramine	reported	nr	nr	nr	common	reported
colesevelam (Welchol)	5 (5)	3 (6)	3.9 (3.1)	nr	11 (7)	8 (3)
colestipol (Colestid)	reported	reported	reported	reported	common	reported
Cholesterol Absorption Inhibitor						
ezetimibe (Zetia)	3 (2.8)	4 (4)	nr	nr	nr	nr
Fibric Acids						
fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide)	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	2-8 (1.4)	2.1 (1.4)	reported
fenofibric acid (Fibricor)	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	7.5 (1.4)	2.1 (1.4)	3.7
fenofibric acid (Trilipix)	4.6 (4.4)	3.4 (2.5)	3.2 (2.7)	7.5 (1.4)	2.1 (1.4)	3.7
gemfibrozil (Lopid)	9.8 (5.6)	nr	1.2 (1.1)	1	1.4 (1.3)	19.6 (11.9)

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Adverse Effects (continued)

Drug	Abdominal Pain	Back pain	Headache	Abnormal LFTs	Constipation	Dyspepsia
Niacin						
niacin ER (Niaspan)	2-5 (3)	nr	8-11 (15)	reported	nr	2-5 (8)
niacin IR (Niacor)	nr	nr	reported	reported	nr	reported
Omega-3 Fatty Acids						
icosapent ethyl (Vascepa)	reported	nr	nr	nr	reported	nr
omega-3-acid ethyl esters (Lovaza)	nr	nr	nr	reported	reported	3.1 (2.6)
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors						
alirocumab (Praluent)	nr	nr	nr	2.5 (1.8)	nr	nr
evolocumab (Repatha)	nr	2.3 (2.2)	4 (3.6)	nr	nr	nr

nr = not reported; LFTs = liver function tests
Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive. Incidences for the placebo group are indicated in parentheses.

ACL Inhibitor: Other common adverse events reported for bempedoic acid (Nexletol) versus placebo, respectively, include upper respiratory tract infection (4.5% versus 4%), muscle spasms (3.6% versus 2.3%), hyperuricemia (3.5% versus 1.1%), bronchitis (3% versus 2.5%), pain in extremity (3% versus 1.7%), and anemia (2.8% versus 1.9%).

ACL Inhibitor/Cholesterol Absorption Inhibitor: The most common adverse events seen with bempedoic acid/ezetimibe (Nexlizet) therapy were comparable to adverse events seen in individual studies of both bempedoic acid and ezetimibe. Common adverse effects seen with bempedoic acid/ezetimibe versus placebo, respectively, but not in the individual bempedoic acid and ezetimibe trials, were urinary tract infection (5.9% versus 2.4%), nasopharyngitis (4.7% versus 0%), constipation (4.7% versus 0%). The most common adverse event leading to treatment discontinuation with bempedoic acid/ezetimibe was oral discomfort (2% versus 0%).

Apolipoprotein B synthesis inhibitor: Other commonly reported adverse reactions for lomitapide were gastrointestinal in nature, reported by 93% of patients on lomitapide in clinical trials. Other adverse effects reported include influenza (21%), decreased weight (24%), chest pain (24%), fatigue (17%), and pharyngolaryngeal pain (14%).

Bile acid sequestrants: Less flatulence, constipation, dyspepsia, and other gastrointestinal effects have been reported with colesevelam than with cholestyramine and colestipol. However, no direct comparisons are available.[227] Colesevelam can increase triglycerides in combination with insulin or sulfonylureas. In the diabetes trials, the overall incidence of hypoglycemia was 3% in patients on colesevelam versus 2.3% in placebo-treated patients.

Cholesterol Absorption Inhibitor: Cases of myopathy and rhabdomyolysis have been reported in patients treated with ezetimibe co-administered with a statin and with ezetimibe administered alone. Risk for skeletal muscle toxicity increases with higher doses of statin, advanced age (> 65 years), hypothyroidism, renal impairment, and depending on the statin used, concomitant use of other drugs.

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A systematic review of 18 randomized controlled trials of combination statin and ezetimibe trials was performed to assess risk in 14,471 patients.[228] Compared with statin monotherapy, combination therapy did not result in significant absolute increases in risks of myalgias, creatine kinase increases, rhabdomyolysis, transaminase increases, gastrointestinal adverse events, or discontinuations because of an adverse event. This systematic review showed that the addition of ezetimibe to statin therapy did not increase the risk of myalgias, creatine kinase levels, rhabdomyolysis, transaminase levels, gastrointestinal adverse events, or discontinuations due to adverse events.

Fibric acids: Fibric acids may cause cholelithiasis. Fenofibrate and fenofibric acid may also cause myositis, myopathy, and rhabdomyolysis; this risk may be further increased when given concomitantly with statins.

Fenofibrate use is associated with reversible elevations in serum creatinine. The clinical significance of this is unknown. Renal function should be monitored in patients with or at risk for renal insufficiency, such as the elderly and patients with diabetes. In a study that assessed renal outcomes in elderly adults within 90 days of a new fibrate prescription, patients who received fibrates (n=19,072) were more likely to be hospitalized for an increase in serum creatinine level (adjusted odds ratio, 2.4 [95% CI, 1.7 to 3.3]) and were more likely to consult a nephrologist (absolute risk difference, 0.15% [CI, 0.01 to 0.29]; adjusted odds ratio, 1.3 [CI, 1 to 1.6]), than patients who received ezetimibe (n=61,831).[229] There were no differences between groups in the risk for all-cause mortality or receiving dialysis for severe acute kidney injury. In a subpopulation of 1,110 patients (fibrates, n=220; ezetimibe, n=890), 9.1% of fibrate users and 0.3% of ezetimibe users had an increase in serum creatinine level of at least 50%. Risks were greater among fibrate users with chronic kidney disease.

Niacin: Flushing has been reported to occur in up to 88% of patients receiving niacin ER. Hyperglycemia and/or hyperuricemia (and/or gout) have also been associated with the use of niacin.

Omega-3-acids: In hypertriglyceridemia clinical trials, other adverse effects for icosapent ethyl occurring ≥ 1% more than placebo were reported included arthralgia and oropharyngeal pain. Cardiovascular outcomes trials reported additional adverse effects that occurred at an incidence ≥ 1% than seen in placebo, including musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation. Postmarketing adverse reactions reported for icosapent ethyl include diarrhea, increased triglycerides, abdominal discomfort, and pain in the extremities.

In addition, icosapent ethyl has been associated with an increased risk of atrial fibrillation or flutter requiring hospitalization for ≥ 24 hours. In patients with either CVD or diabetes and ≥ 1 risk factor for CVD, 127 (3%) patients receiving icosapent ethyl developed atrial fibrillation or flutter requiring hospitalization versus 84 (2%) patients receiving placebo (hazard ratio [HR], 1.5; 95% CI, 1.14 to 1.98).

An increased bleeding risk has also been associated with icosapent ethyl. In clinical trials, bleeding events occurred in 482 (12%) participants receiving icosapent ethyl versus 404 (10%) of those receiving placebo. The incidence of serious bleeding events was also higher for icosapent ethyl treated patients, occurring in 111 (3%) patients versus 85 (2%) patients receiving placebo.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors: Common adverse reactions with the PCSK9 inhibitors include nasopharyngitis, injection site reactions, upper respiratory tract infection/inflammation, urinary tract infections, diarrhea, and myalgia.

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Similar incidence of neurocognitive events were reported for the PCSK9 inhibitors compared to placebo (0.8% and 0.7% of patients treated with alirocumab and placebo, respectively; ≤ 0.2% of patients treated with evolocumab or placebo).

In a cardiovascular outcomes trials with over 18,000 patients, 5.5% of patients treated with alirocumab developed anti-drug antibodies (ADA) compared with 1.6% of patients treated with placebo; consistent ADA, defined as ≥ 2 consecutive samples separated by ≥ 16 weeks, were reported in 0.7% and 0.4% of patients in each group, respectively, and neutralizing antibodies (Nab) were found in 0.5% and < 0.1% of patients in each group, respectively. While LDL-C reduction was typically similar in patients with or without ADA, some patients treated with alirocumab with persistent ADA or Nab experienced diminished LDL-C efficacy. In clinical trials, 0.1% of patients treated with evolocumab tested positive for binding antibody development; however, none of these patients who were tested further for Nab tested positive. There was no evidence that the presence of anti-drug binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of evolocumab. The long-term consequences of continuing treatment in the presence of persistent Nab are unknown. The ability to detect of antibodies is dependent on several factors; therefore, comparison of the incidence of antibodies between studies or between products may be misleading.

In July 2016, the FDA approved the Pushtronex™ on-body infusion device as a single-injection option for the delivery of evolocumab (Repatha) 420 mg once monthly dose. Adverse effects reported were similar to those for the 420 mg dose delivered as 3 consecutive SC injections.[230]

SPECIAL POPULATIONS[231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253]

Pediatrics

Many of the products in the Other Lipotropics category do not have safety and effectiveness data in the pediatric population. Limited data are available regarding use in children for cholestyramine and colestipol.[254] Pediatric patients have been reported to experience hyperchloremic metabolic acidosis or gastrointestinal obstruction with the use of cholestyramine.[255] Colesevelam (Welchol) is approved to reduce LDL-C in boys and postmenarchal girls, aged 10 to 17 years, with HeFH as monotherapy or in combination with a statin. Colesevelam has not been studied in children < 10 years. Ezetimibe (Zetia) has been used in a limited number of children ages ≥ 10 years, but the safety and effectiveness have not been established in patients < 10 years of age. Niacin has been used safely for the treatment of nutritional deficiencies; however, safety and effectiveness of niacin for the treatment of hyperlipidemias have not been established in pediatrics. Safety and efficacy of fibric acids (fenofibrate, fenofibric acid, and gemfibrozil), lomitapide (Juxtapid), omega-3-acid ethyl esters (Lovaza), icosapent ethyl (Vascepa), bempedoic acid (Nexletol), and bempedoic acid/ezetimibe (Nexlizet) have not been established in pediatrics.

The combination ezetimibe/simvastatin demonstrated a greater mean percent reduction in LDL-C compared to simvastatin alone (-15% [95% CI, -18 to -12]) in boys and postmenarchal girls 10 to 17 years of age.[256]

In addition, in a clinical study colesevelam 3.8 g/day significantly decreased plasma levels of LDL-C (-13%), total cholesterol (-7%), and significantly increased HDL-C (+6%) compared to placebo (p≤0.05 for all comparisons) in boys and postmenarchal girls 10 to 17 years of age.[257]

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The safety and efficacy of alirocumab (Praluent) in pediatric patients have not been established. The safety and efficacy of evolocumab (Repatha) for the treatment of adolescents ages 13 to 17 years old with HoFH who require additional LDL-C lowering was established in a placebo-controlled, 12-week trial (n=10 [n=7, evolocumab; n=33 placebo]). Additional details on this trial, which also included adults, are described in the Clinical Studies section below. The safety and efficacy of evolocumab in pediatric patients with primary hyperlipidemia or HeFH or in patients < 13 years old with HoFH have not been established. The Pushtronex on-body infusion should only be used in children 13 to 17 years of age under adult supervision, as instructed by a healthcare professional.

Pregnancy

There are no available data on use of bempedoic acid in pregnant women to assess risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bempedoic acid (Nexletol) and bempedoic acid/ezetimibe (Nexlizet) should be discontinued when pregnancy is recognized unless its benefits outweigh the potential risk to the fetus.

Previously Pregnancy Category X, labeling for lomitapide (Juxtapid) has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and states that use may cause fetal harm and therefore is contraindicated in pregnancy. Females of reproductive potential should have a negative pregnancy test before starting lomitapide therapy and should use effective contraception during therapy. Females on lomitapide who become pregnant should stop therapy immediately and notify their healthcare provider.

Previously Pregnancy Category B, labeling for colesevelam (Welchol) has been updated to comply with the PLLR and states the product is not absorbed systemically following oral administration, and maternal use is not expected to result in fetal exposure to the drug. Limited available data on the use of colesevelam are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage.

Niacin is Pregnancy Category A for recommended daily allowance nutrient amounts; however, for the treatment of hyperlipidemia, niacin IR (Niacor) is considered Pregnancy Category C. Previously Pregnancy Category C, labeling for niacin extended-release (Niaspan) has been updated to comply with the PLLR and states therapy should be discontinued once pregnancy is recognized when used for treating hyperlipidemia and the risks versus benefits should be considered for use during pregnancy when used for treating hypertriglyceridemia.

Previously considered Pregnancy Category C, labeling has been updated to comply with the PLLR and advises data are insufficient for alirocumab, evolocumab, fenofibrate (Fenoglide, Fibricor, Tricor, Trilipix), gemfibrozil (Lopid), icosapent ethyl (Vascepa), omega-3-acid ethyl esters (Lovaza) in pregnant women to determine drug-associated fetal or maternal risks.

The remaining products in this class are Pregnancy Category C.

Pregnancy exposure registries monitor pregnancy outcomes in women exposed to alirocumab and evolocumab during pregnancy.

Gender

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was a double-blind, placebo-controlled study that evaluated if fenofibrate reduced major CV events in patients with type 2 diabetes and whether there were gender differences in fenofibrate response.[258] A total of 3,657 women and

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6,138 men with type 2 diabetes and not on statin therapy received either fenofibrate 200 mg/day or placebo for 5 years. LDL-C, HDL-C, non-HDL-C, and apolipoproteins (apo) A-1 and B improved in both men and women (all p<0.001). A greater reduction was seen in women for all measures, except apo A-1. Fenofibrate reduced total CV outcomes (CV death, fatal and non-fatal stroke, and carotid and coronary revascularization) by 30% in women (p=0.008) and 13% in men (p=0.07).

Hepatic/Renal Impairment

No dose adjustment of bempedoic acid (Nexletol) is required in patients with mild or moderate hepatic impairment. Bempedoic acid has not been studied in those with severe hepatic impairment (Child-Pugh C). Bempedoic acid/ezetimibe (Nexlizet) is not recommended with moderate to severe hepatic impairment (Child-Pugh B or C).

No dose adjustment of bempedoic acid or bempedoic acid/ezetimibe is required in patients with mild or moderate renal impairment. Data are lacking on use in patients with severe impairment and bempedoic acid has not been studied with end-stage renal disease.

Fenofibrates (Antara, Fenoglide, Lipofen, Tricor, Triglide) and fenofibric acid (Fibricor, Trilipix) should be dose adjusted in renal impairment, unless severe impairment, when use is contraindicated. Their use has not been evaluated in hepatic impairment, but is contraindicated in hepatic dysfunction including patients with primary biliary cirrhosis or unexplained persistent liver function abnormalities.

Ezetimibe is not recommended in moderate to severe hepatic impairment.

No dosage adjustment of ezetimibe is necessary with renal impairment. When ezetimibe is given with simvastatin in patients with moderate to severe renal impairment (estimated glomerular filtration [eGFR] < 60 mL/min/1.73 m^2), doses of simvastatin > 20 mg should be used cautiously and with close monitoring for myopathy.

Niacin-containing products should be used with caution in patients with renal impairment, past history of liver disease, and in patients who consume substantial quantities of alcohol. Active liver disease, unexplained transaminase elevations, and significant or unexplained hepatic dysfunction are contraindications to the use of niacin.

Lomitapide is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C). Lomitapide exposure is significantly increased in patients with mild hepatic impairment (Child-Pugh A) or with end-stage renal disease (ESRD) receiving dialysis; therefore, lomitapide dosage should not exceed 40 mg daily. Although not studied, it is possible that lomitapide exposure is increased in those patients with mild, moderate, or severe renal impairment, not on dialysis; therefore, caution should be used.

Monitor liver function (ALT, AST) in patients with hepatic impairment periodically during therapy with omega-3-acid ethyl esters and icosapent ethyl (Vascepa).

No dose adjustment is necessary for patients with mild to moderate hepatic or renal impairment using alirocumab or evolocumab. Neither alirocumab nor evolocumab have been studied in patients with severe hepatic or renal impairment.

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DOSAGES[259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281]

Drug	Availability	Dose	Comments
ACL Inhibitor			
bempedoic acid (Nexletol)	180 mg tablets	180 mg once daily	Take with or without food
ACL Inhibitor/Cholesterol Absorption Inhibitor			
bempedoic acid/ ezetimibe (Nexlizet)	180 mg/10 mg tablets	180 mg/10 mg once daily	Take with or without food Swallow tablets whole
Apolipoprotein B Synthesis Inhibitor			
lomitapide (Juxtapid)	5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg capsules	Initiate with 5 mg daily; Titrate to 10 mg daily after ≥ 2 weeks, then 4-week intervals to 20 mg, 40 mg, 60 mg; Do not exceed 60 mg per day*	Swallow capsules whole Take with water and without food, at least 2 hours after the evening meal
Bile Acid Sequestrants			
cholestyramine (Questran, Questran Light)	powder for oral suspension†	1 to 2 packets or scoopfuls twice daily	Mix with 2 to 6 ounces of water or pulpy fruit (applesauce)
colesevelam (Welchol)	625 mg tablets	Hyperlipidemia or Type 2 DM: 3,750 mg daily in 1 or 2 divided doses	May be increased to 4,375 mg daily Take with meals Oral suspension may be mixed with water, fruit juice, or diet soft drinks prior to ingestion
	3,750 mg packet powder for oral suspension		
colestipol (Colestid)	1 g tablets	2 g once or twice daily	Increase by 2 g at 1- to 2-month intervals to a maximum of 16 g daily
	5 g granule packets and 7.5 g flavored granule packs (each 7.5 g packet contains 5 g colestipol hydrochloride)	5 g to 30 g daily	Increase daily dose by 5 g at 1- to 2-month intervals
Cholesterol Absorption Inhibitors			
ezetimibe (Zetia)	10 mg tablets	10 mg daily	Take with or without food
Fibric Acids			
fenofibrate	67 mg, 134 mg, 200 mg capsules	67 mg to 200 mg daily	Must be taken with food
	54 mg, 160 mg tablets	54 mg to 160 mg daily	
fenofibrate (Antara)	30 mg, 90 mg capsule (brand only)‡	30 mg to 90 mg daily	Take without regard to meals
	43 mg, 130 mg capsules (generic only)	43 mg to 130 mg daily	

* Patients with ESRD on dialysis or with baseline mild hepatic impairment should not exceed lomitapide 40 mg daily.

† Prevalite (cholestyramine/aspartame) powder for oral suspension, by Upsher-Smith, was approved under an abbreviated new drug application (ANDA).

‡ Antara 43 mg and 130 mg capsules have been discontinued and replaced by Antara 30 mg and 90 mg capsules.

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Dosages (continued)

Drug	Availability	Dose	Comments
Fibric Acids (*continued*)			
fenofibrate (Fenoglide)	40 mg, 120 mg tablets	40 mg to 120 mg daily	Take with food
fenofibrate (Lipofen)	50 mg, 150 mg capsules	50 mg to 150 mg daily	Take with food
fenofibrate (Tricor)	48 mg, 145 mg tablets	48 mg to 145 mg daily	Take without regard to meals
fenofibrate (Triglide)	160 mg tablets	50 mg to 160 mg daily	Take without regard to meals
fenofibric acid (Fibricor)	35 mg, 105 mg tablets	35 mg to 105 mg daily	Take without regard to meals
fenofibric acid (Trilipix)	45 mg, 135 mg delayed-release capsules	45 mg to 135 mg daily	Take without regard to meals
gemfibrozil (Lopid)	600 mg tablets	600 mg twice daily	Take 30 minutes prior to meal
Niacin			
niacin ER (Niaspan)	500 mg, 750 mg, 1,000 mg tablets	500 mg to 2,000 mg at bedtime§	Titrate dose up every 4 weeks May pre-administer aspirin to reduce flushing Take at bedtime after low-fat snack
niacin IR (Niacor)	500 mg tablets	1 g to 2 g twice or 3 times daily§	May pre-administer aspirin to reduce flushing Take at bedtime after low-fat snack
Omega-3 Fatty Acids			
icosapent ethyl (Vascepa)	0.5 g and 1 g capsules	2 g twice daily	Take with food Swallow capsules whole
omega-3-acid ethyl esters (Lovaza)	1 g capsules‖	4 g daily in 1 or 2 divided doses	Take with meal(s) Swallow capsules whole
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors			
alirocumab (Praluent)	75 mg/1 mL and 150 mg/1 mL single-use prefilled pen	75 mg subcutaneously (SC) once every 2 weeks; may be increased to a maximum of 150 mg administered every 2 weeks; and alternative starting dose is 300 mg (2 x 150 mg SC injections) may be given every 4 weeks In patients with HeFH undergoing LDL apheresis: 150 mg once every 2 weeks (administer without regard to timing of apheresis)	Patients can self-administer the pen or syringe with proper training; Administration should be in the thigh, abdomen, or upper arm; rotate the injection site with each injection

§ Regular and extended-release formulations of niacin are not interchangeable.

‖ Triklo (omega-3-acid ethyl esters), by Key Therapeutics, was approved under an abbreviated new drug application (ANDA). It is available as a 1 gram liquid filled capsule.

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Dosages (continued)

Drug	Availability	Dose	Comments
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors *(continued)*			
evolocumab (Repatha)	140 mg/1 mL prefilled syringe or SureClick® auto-injector 420 mg/3.5 mL single-use Pushtronex system (on-body infusor with prefilled cartridge)¶	Established CVD or HeFH or with primary hyperlipidemia: 140 mg subcutaneously once every 2 weeks or 420 mg once monthly; HoFH: 420 mg once monthly	Patients can self-administer the pen, syringe, or Pushtronex system with proper training; administer in the thigh, abdomen, or upper arm; Rotate the injection sites The 420 mg dose may be delivered via: ▪ Prefilled autoinjector or syringe – administer three 140 mg/mL injections SC consecutively within 30 minutes ▪ Pushtronex system – administer 420 mg SC dose over 5 minutes

¶ The Repatha Pushtronex system is a single-use infusor device that is attached to the skin to provide hands-free delivery of evolocumab 420 mg in a single SC dose. Moderate physical activity can be done during the injection process (e.g., walking, reaching, bending).

Bempedoic acid and bempedoic acid/ezetimibe are given in combination with maximally tolerated statin therapy. Lipid levels should be assessed within 8 to 12 weeks after starting therapy with bempedoic acid or bempedoic acid/ezetimibe.

Lomitapide doses should be reduced or withheld if transaminase levels increase to ≥ 3 x ULN during treatment. When levels resolve to < 3 x ULN, consider resuming lomitapide at reduced doses.

LDL-C levels should be measured within 4 to 8 weeks of initiating or titrating therapy with PCSK9 inhibitors to assess response and adjust the dose, as needed.

For missed doses of alirocumab the patient should administer the injection within 7 days from the missed dose and then resume the original dosing schedule. If the missed dose is not administered within 7 days, then the patient should wait until the next dose on the original schedule. If a dose of evolocumab is missed, the patient should administer the dose as soon as possible if there are more than 7 days until the next scheduled dose, or omit the missed dose and administer the next dose according to the original schedule.

Alirocumab and evolocumab should be refrigerated and may be kept at room temperature in the original carton for up to 30 days. Alirocumab should be allowed to warm to room temperature for 30 to 40 minutes prior to use. If refrigerated, the Repatha Pushtronex (evolocumab) infusor should naturally reach room temperature over 45 minutes prior to use.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human

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participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship funding must be considered, the studies in this review have also been evaluated for validity and importance.

The effects of the drugs in this class on lipids are well documented. To date, however, clinical outcomes have not been established for bempedoic acid (Nexletol), bempedoic acid/ezetimibe (Nexlizet), colesevelam (Welchol), colestipol (Colestid), fenofibrates, lomitapide (Juxtapid), or prescription strength omega-3-acid ethyl esters (Lovaza).[282,283,284,285,286,287,288,289,290]

bempedoic acid (Nexletol)

The CLEAR trial program included four phase 3, double-blind, randomized clinical trials evaluating efficacy and safety of bempedoic acid. The CLEAR Harmony 52-week trial enrolled adults with ASCVD, HeFH, or both. Baseline LDL-C levels were ≥ 70 mg/dL while on maximally tolerated stain therapy with or without additional lipid-lowering therapies.[291] Patients were randomized to bempedoic acid 180 mg once daily (n=1,488) or matching placebo (n=742). Mean baseline LDL-C was 103.2 mg/dL. Mean age was 66.1 years. Key exclusion criteria were the use of gemfibrozil or simvastatin at doses > 40 mg per day. The use of a PCSK9 inhibitor was permitted after week 24 for patients with LDL-C > 170 mg/dL and an LDL-C increase by ≥ 25% from baseline. At week 12, bempedoic acid resulted in the mean reduction of LDL-C by 19.2 mg/dL (difference from placebo in change from baseline, -18.1%; 95% confidence interval [CI], -18.2 to -14; p<0.001). Significant differences in changes from baseline compared to placebo were also seen in non-high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), apolipoprotein B (apo-B), and high-sensitivity C-reactive protein (hsCRP) at week 12 (p<0.001 for all). Effect was seen through week 52 of the study. Efficacy did not depend on type or intensity of background lipid-lowering therapy.

The CLEAR Wisdom 52-week trial included adults with ASCVD, HeFH, or both. Baseline LDL-C levels were ≥ 70 mg/dL while on maximally tolerated statin therapy.[292] Patients were randomized to bempedoic acid 180 mg once daily (n=522) or matching placebo (n=257) added to maximally tolerated lipid lowering therapy. At baseline, mean LDL-C level was 120.4 mg/dL. Mean age was 64 years. At week 12, the difference in mean percent change in LDL-C from baseline between bempedoic acid and placebo was -17.4% (95% CI, -21 to -13.9; p<0.001).

The CLEAR Serenity trial assessed 345 patients with hypercholesterolemia and a history of intolerance to ≥ 2 statins. Baseline LDL-C levels were ≥ 130 mg/dL for primary prevention patients and ≥ 100 mg/dL for patients with HeFH while on maximally tolerated statin therapy.[293] Patients were randomized to bempedoic acid 180 mg or placebo once daily for 24 weeks. Stable background lipid-lowering therapy was continued. Mean age was 65.2 years and mean baseline LDL-C was 157.6 mg/dL. At week 12, bempedoic acid significantly reduced LDL-C from baseline (difference from placebo, −21.4% [95% CI, −25.1 to −17.7]; p<0.001). Significant reductions from baseline compared to placebo were also seen with non-HDL-C, TC, apo-B, and hsCRP (p<0.001 for all).

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The CLEAR Tranquility trial enrolled adults with a history of statin intolerance and an LDL-C ≥ 100 mg/dL while on stable lipid-lowering therapy.[294] After a 4-week run-in period with ezetimibe 10 mg/day, patients were randomized to bempedoic acid 180 mg once daily (n=181) or placebo (n=88) as add-on to background lipid-lowering therapy that included ezetimibe 10 mg/day. The mean baseline LDL-C was 127.6 mg/dL. The mean age was 63.8 years. The change in LDL-C from baseline to week 12 was significantly greater with bempedoic acid compare to placebo (difference from placebo, -28.5% [95% CI, -34.4 to -22.5; p<0.001). Significant reductions in LDL-C with bempedoic acid compared to placebo were recorded at week 4. In addition, significant reductions from baseline compared to placebo were also observed with non-HDL-C, TC, apo-B, and hsCRP (p<0.001 for all). The study demonstrated minimal effect on triglyceride levels.

bempedoic acid (Nexletol) and bempedoic acid/ezetimibe (Nexlizet)

The efficacy and safety of bempedoic acid and bempedoic acid/ezetimibe were assessed in a phase 3, double-blind clinical trial that enrolled 301 adults with ASCVD, HeFH, or multiple CVD risk factors.[295] Patients were randomized 2:2:2:1 to once daily fixed-dose combination of bempedoic acid/ezetimibe 180 mg/10 mg, bempedoic acid 180 mg, ezetimibe 10 mg, or placebo as add-on to stable background statin therapy for 12 weeks. The mean LDL-C was 149.8 mg/dL at baseline. At week 12, all treatment groups resulted in significant reductions in LDL-C compared to placebo (fixed-dose combination: –36.2%; bempedoic acid alone: –17.2%; ezetimibe alone: –23.2%; placebo: 1.8%; p<0.001 for all compared to placebo).

cholestyramine

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), a multicenter, double-blind study, tested the efficacy of cholesterol lowering in reducing risk of CHD.[296,297] A total of 3,806 asymptomatic middle-aged (35 to 59 years) men with primary hypercholesterolemia were randomized to receive cholestyramine 24 g/day or placebo for an average of 7.4 years. Both groups followed a moderate cholesterol-lowering diet. The cholestyramine group experienced average reductions in total-C of 13.4% and in LDL-C of 20.3%. The cholestyramine group experienced a 19% reduction in risk (p<0.05) of the primary composite endpoint of definite CHD death and/or definite nonfatal MI; this reflected a 24% reduction in definite CHD death and a 19% reduction in nonfatal MI. The cumulative 7-year incidence of the primary endpoint was 7% in the cholestyramine group and 8.6% in the placebo group. In addition, the incidence rates were reduced for new positive exercise tests (by 25% compared to placebo; p<0.001) and new onset angina (by 20%; p<0.01). The incidence of coronary bypass surgery was similar in each group. The risk of death from all causes was reduced by 7% (p=not significant [NS]) in the cholestyramine group; the magnitude of this decrease was less than for CHD endpoints because of a greater number of violent and accidental deaths in the cholestyramine group.

cholestyramine, gemfibrozil, and niacin IR (Niacor)

A randomized, double-blind, placebo-controlled trial assessed the effects of gemfibrozil, niacin immediate-release, and cholestyramine on the composite outcome of MI, transient ischemic attack or stroke, CV death, CV procedures, or hospitalization for angina.[298] A total of 143 military retirees with low HDL-C (mean 34 mg/dL) and documented CAD were randomized to the combination of therapy or placebos. Active treatment included gemfibrozil 600 mg twice daily, niacin 500 mg titrated to 3,000 mg daily, and cholestyramine 2 gm titrated to 16 gm daily. Aggressive dietary and lifestyle changes were followed for 6 months prior to randomization. Cardiac angiography was performed at baseline and

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after 30 months of follow-up. The active treatment group experienced a total-C reduction of 20% (95% CI, 14.8 to 24.3), LDL-C reduction of 26% (95% CI, 19.1 to 33.7), triglyceride (TG) reduction of 50% (95% CI, 40.5 to 59.2), and an increase in HDL-C of 36% (95% CI, 28.4 to 43.5). The composite endpoint was reached by 26.4% of the placebo group compared to 12.7% of the active treatment group, an absolute difference of 13.7% (95% CI, 0.9 to 26.5). There were no significant differences in the individual clinical event rates between the 2 small groups. On repeat cardiac angiography, the active treatment group was observed to have slight regression, whereas the placebo group experienced progression over the 30 months. Flushing, skin rash, and GI intolerance were more common in the active treatment group, and flushing problems could have led to the possibility of unblinding.

colesevelam (Welchol) and metformin, sulfonylurea, and insulin

Efficacy of colesevelam in type 2 diabetes mellitus was evaluated in 3 double-blind, placebo-controlled trials in combination with metformin, sulfonylurea, or insulin.[299] A total of 1,018 patients with baseline hemoglobin A1c (HbA1c) of 7.5% to 9.5% took colesevelam 3.75 g/day as 3 tablets twice daily with meals or as 6 tablets with dinner for 26 weeks. In all 3 trials, HbA1c was reduced by 0.5% compared to placebo ($p<0.001$ for all comparisons). Colesevelam increased TG levels in patients taking concurrent insulin or sulfonylurea but not in the metformin study.

A 26-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated the effects of colesevelam 3.75 g daily in 316 patients with inadequately controlled type 2 diabetes mellitus (baseline HbA1c of 8.1%), who were receiving metformin monotherapy or metformin combined with additional oral anti-diabetes drugs.[300] Colesevelam lowered the mean HbA1c level by -0.54% compared with placebo at week 26 ($p<0.001$). Similar results were observed in the metformin monotherapy (-0.47%, $p=0.002$) and combination therapy cohorts (-0.62%, $p<0.001$). Colesevelam also significantly reduced fasting plasma glucose (-13.9 mg/dL, $p=0.01$), total-C (-7.2%, $p<0.001$), LDL-C (-15.9%, $p<0.001$), and apo B (-7.9%, $p<0.001$). TG, HDL-C, and apolipoprotein A-I levels were not statistically significantly increased.

colesevelam (Welchol) and insulin

A 16-week, randomized, double-blind, placebo-controlled, parallel group, multicenter study of 287 patients with type 2 diabetes mellitus evaluated the efficacy and safety of colesevelam 3.75 g/day in patients already receiving insulin alone or in combination with oral antidiabetic agents with inadequate glycemic control (mean baseline HbA1c 8.3%).[301] The mean (SE) change in HbA1c was -0.41% (0.07%) versus 0.09% (0.07%) for colesevelam versus placebo, respectively. The treatment difference was 0.5% (SE, 0.09%; 95% CI, -0.68 to -0.32; $p<0.001$). There was a 12.8% reduction in LDL-C levels in the colesevelam group versus placebo ($p<0.001$). Median TG levels increased significantly in the colesevelam group.

colesevelam (Welchol) and ezetimibe (Zetia)

A randomized, double-blind, placebo-controlled, parallel group, multicenter study compared colesevelam 3.8 gm/day plus ezetimibe 10 mg daily to placebo plus ezetimibe 10 mg daily in 86 patients for 6 weeks.[302] The primary endpoint was the mean percentage change in LDL-C reduction and secondary endpoints were mean absolute change in LDL-C, mean absolute and mean percentage change in HDL-C, non-HDL-C, TC, apo A-I, and apo B, and mean absolute change and percentage changes in TG and C-reactive protein (CRP). Colesevelam plus ezetimibe produced a mean percentage change in LDL-C of -32.3% versus -21.4% with ezetimibe monotherapy ($p<0.0001$). The combination

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therapy was significantly more effective than ezetimibe alone in reducing total-C, non-HDL-C, and apo-B, and increasing apo A-I (p<0.005 for all). Neither regimen significantly increased TG (p=NS). Both treatment arms were generally well tolerated.

colesevelam (Welchol) in pediatrics

The safety and efficacy of colesevelam in pediatric patients were evaluated in an 8-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, study followed by an open-label phase, in 194 boys and postmenarchal girls 10 to 17 years of age with HeFH, taking a stable dose of an FDA-approved statin (with LDL-C > 130 mg/dL) (24% of patients) or naïve to lipid-lowering therapy (with LDL-C > 160 mg/dL) (76% of patients).[303] The mean baseline LDL-C was approximately 199 mg/dL. During the double-blind treatment period, patients were assigned randomly to treatment: colesevelam 3.8 g/day (n=64), colesevelam 1.9 g/day (n=65), or placebo (n=65). A total of 186 patients completed the double-blind treatment period. After 8 weeks of treatment, colesevelam 3.8 g/day significantly decreased plasma levels of LDL-C (-13%), total cholesterol (-7%), and significantly increased HDL-C (+6%) compared to placebo (p≤0.05 for all comparisons). There was a non-significant increase in TG (+5%) versus placebo. Patients were treated with colesevelam 3.8 g/day during the open-label treatment period. A total of 173 patients completed 26 weeks of treatment. Results at week 26 were consistent with those at week 8.

ezetimibe (Zetia) and fenofibrate

A randomized, double-blind, placebo-controlled, parallel-group, multicenter, 12-week study of 625 patients with mixed hyperlipidemia compared fenofibrate 160 mg/day, ezetimibe 10 mg/day, or the combination of fenofibrate 160 mg/day and ezetimibe 10 mg/day.[304] At baseline and at 12 weeks, the Vertical Auto Profile II method was used to measure the cholesterol associated with 2 very low-density lipoprotein (VLDL) subfractions (VLDL-C1 + 2 and VLDL-C3), intermediate-density lipoproteins (IDL-C), and 4 LDL-C subfractions (LDL-C1 through LDL-C4, from most buoyant to most dense), lipoprotein (Lp) (a), and 2 HDL-C subfractions (HDL-C2 and HDL-C3). The LDL-C particle size was determined using segmented gradient gel electrophoresis. Fenofibrate reduced cholesterol mass within VLDL-C, IDL-C, and dense LDL-C (primarily LDL-C4) subfractions, and increased cholesterol mass within the more buoyant LDL-C2 subfraction, consistent with a shift to a more buoyant LDL-C peak particle size. Ezetimibe reduced cholesterol mass within all of the apolipoprotein B-containing particles (e.g., VLDL-C, IDL-C, and LDL-C) but did not lead to a shift in the LDL-C particle size distribution profile. Co-administration of fenofibrate and ezetimibe promoted more pronounced reductions in VLDL-C, IDL-C, and LDL-C, and a preferential decrease in dense LDL-C subfractions. Fenofibrate and combination therapy promoted similar increases in HDL-C2 and HDL-C3.

ezetimibe (Zetia) plus simvastatin (Zocor) versus simvastatin (Zocor) monotherapy in pediatrics

In a multi-center, double-blind, controlled study followed by an open-label phase, 142 boys and 106 postmenarchal girls, 10 to 17 years of age, with HeFH were randomized to receive either ezetimibe co-administered with simvastatin or simvastatin monotherapy.[305] The mean baseline LDL-C value was 225 mg/dL in the combination group compared to 219 mg/dL in the monotherapy group. The patients received combination of ezetimibe and simvastatin (10 mg, 20 mg, or 40 mg) or simvastatin monotherapy (10 mg, 20 mg, or 40 mg) for 6 weeks, co-administered ezetimibe/simvastatin 10/40 mg or simvastatin 40 mg monotherapy for the next 27 weeks, and open-label co-administered ezetimibe

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and simvastatin (10 mg, 20 mg, or 40 mg) for 20 weeks thereafter. At week 6, the mean percent difference between treatment groups for LDL-C was -15% (95% CI, -18 to -12). Results at week 33 were consistent with those at week 6.

fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide)

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9,795 patients with type 2 diabetes and no signs of prior CV disease were randomized to fenofibrate 200 mg/day or placebo for a median of 5 years.[306] Patients were 50 to 75 years, had total-C of 116 to 251 mg/dL, and did not take statin therapy prior to study enrollment. In the double-blind trial, the primary outcome of coronary events (CHD death and non-fatal MI) occurred in 5.9% and 5.2% of placebo and fenofibrate groups, respectively, for a relative risk reduction of 11% (p=0.16). The fenofibrate group had a 24% relative risk reduction for non-fatal MI with a nonsignificant increase in CHD mortality. The excess of CHD deaths in the fenofibrate group (110 versus 93 events in the placebo group) was mostly due to an increase in sudden cardiac death (70 versus 64 events, respectively). The secondary endpoint of total CV events (CV mortality, MI, stroke, and coronary and carotid revascularization) occurred in 12.5% of patients in the fenofibrate group and 13.9% of patients in the placebo group (p=0.035). This reduction was primarily related to a 24% relative risk reduction in the incidence of MI (p=0.010) and 21% relative risk reduction in coronary revascularization (p=0.003). There was a significant 11% reduction in the secondary outcomes (HR 0.89, 95% CI 0.8 to 0.99, p=0.04). There was a non-significant 11% (HR 1.11, 95% CI 0.95, 1.29, p=0.41) and 19% (HR 1.19, 0.9 to 1.57, p=0.22) increase in total mortality and CHD mortality, respectively, with fenofibrate compared to placebo. By the end of the study, twice as many patients in the placebo group (32%) were receiving statins than in the fenofibrate group (16%; p<0.0001). After adjusting for statin use, investigators estimated that fenofibrate reduced the risk of CHD events by 19% (p=0.01) and of total CV disease events by 15% (p=0.004). Fenofibrate was also associated with less progression of albuminuria (p=0.002). Fenofibrate was well tolerated with a discontinuation rate similar to placebo. Nonsignificant increases in pancreatitis and pulmonary embolism were reported in the fenofibrate group.

The SAFARI study was a randomized, double-blind, active-controlled, multicenter, 18-week (6-week diet and placebo run-in period) study of 618 patients with mixed dyslipidemia.[307] Simvastatin 20 mg daily and fenofibrate 160 mg daily was compared to simvastatin monotherapy 20 mg daily to evaluate efficacy and safety. From baseline to week 12, median TG levels decreased 43% in the combination group and 20.1% in the simvastatin monotherapy group (treatment difference-23.6%, p<0.001). Mean LDL-C decreased 31.2% and 25.8% (treatment difference -5.4%, p<0.001), and HDL-C increased 18.6% and 9.7% (treatment difference 8.8%, p<0.001) in the combination group versus monotherapy group, respectively. No drug-related serious adverse experiences were observed. No cases of clinical myopathy or severe abnormalities in liver function were reported.

The lipid arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a randomized, double-blind, multicenter study of 5,518 patients with type 2 diabetes.[308] After 1 month of open-label simvastatin, patients were randomized to simvastatin plus fenofibrate 160 mg daily or simvastatin plus placebo. The mean age was 62 years, 31% were women, 37% had a prior CV event, mean systolic blood pressure was 134 mm Hg, mean HbA1c was 8.1%, and about 60% were taking a statin prior to enrollment. In the fenofibrate group, LDL-C decreased from 100 to 81 mg/dL, HDL-C increased from 38 to 41.2 mg/dL, and TG decreased from 189 to 147 mg/dL. In the placebo group, LDL-C decreased from 101 to 80 mg/dL (p=0.16 between groups), HDL-C increased from 38 to 40.5 mg/dL

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(p=0.01 between groups), and TG decreased from 186 to 170 mg/dL (p<0.001 between groups). After a mean follow-up of 4.7 years, the annual rate of the primary outcome (first occurrence of nonfatal MI, nonfatal stroke, or death from CV causes) was 2.2% with fenofibrate versus 2.4% with placebo (HR in the fenofibrate group, 0.92; 95% CI, 0.79 to 1.08; p=0.32). There were also no significant differences between the 2 study groups with respect to any secondary outcome. Hazard ratios for the secondary outcomes, including the individual components of the primary outcome, ranged from 0.82 to 1.17 (p≥0.1 for all comparisons). Annual rates of death were 1.5% in the fenofibrate group and 1.6% in the placebo group (HR, 0.91; 95% CI, 0.75 to 1.1; p=0.33). In subgroup analysis, men appeared to benefit, while women appeared to be harmed from fenofibrate therapy (p for interaction=0.01). Also, a high TG (≥ 203 mg/dL)/low HDL-C (≤ 35 mg/dL) profile appeared to non-significantly benefit (p for interaction=0.057) the fenofibrate group versus placebo. Study drug was discontinued due to a decrease in estimated glomerular filtration rate in 2.4% in the fenofibrate group and 1.1% of placebo. Serum creatinine levels increased in the fenofibrate group soon after randomization but then remained constant, compared with placebo. There was no evidence of increased risk of myositis or rhabdomyolysis in the fenofibrate/simvastatin group. The trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI).

fenofibric acid (Trilipix)

In 3, 12-week, randomized, double-blind, multicenter studies of 2,698 patients with mixed dyslipidemia, efficacy, and safety of fenofibric acid in combination with statins to each single agent were reviewed.[309] Moderate doses of rosuvastatin (Crestor®) 10 mg or 20 mg, simvastatin 20 mg or 40 mg, or atorvastatin (Lipitor®) 20 mg or 40 mg were co-administered with 135 mg of fenofibric acid. In the pooled analysis, combination therapy with a low-dose and a moderate-dose statin significantly increased HDL-C (18.1% and 17.5%, respectively) and decreased TG (43.9% and 42%, respectively) compared to the corresponding dose of statin monotherapy (7.4% and 8.7% for HDL-C, -16.8% and -23.7% for TG; p<0.001 for all comparisons). In addition, both doses of combination therapy resulted in mean percent decreases (33.1% and 34.6%, respectively) in LDL-C that is significantly greater than fenofibric acid monotherapy (5.1%, p<0.001).

gemfibrozil

The Helsinki Heart Study, a randomized, double-blind primary prevention study, found that gemfibrozil 1,200 mg/day was associated with a significant reduction in total plasma TG and a significant increase in HDL-C in men ages 40 to 55 years old (n=4,081) compared to placebo.[310,311] Over the 5-year study period, there was a 34% relative risk reduction (p<0.02) in the incidence of cardiac endpoints (MI and cardiac death) with the use of gemfibrozil compared to placebo.[312] At the conclusion of the study, all participants were given the opportunity to receive gemfibrozil for an additional 3.5 years.[313] After the additional open-label period, there was no significant difference in CV or all-cause mortality between the 2 groups.

During screening for the Helsinki Heart Study, approximately 600 dyslipidemic individuals were detected who exhibited signs and symptoms of possible CHD; these subjects were excluded from the primary study.[314] Three-hundred and eleven of these patients were randomized to receive gemfibrozil 1,200 mg/day and 317 subjects to receive placebo over 5 years in double-blind fashion. The primary endpoint, a composite of fatal and non-fatal MI and cardiac deaths, did not differ significantly between the placebo and gemfibrozil groups. The same was true for total mortality. In the study, data were not evaluated for several key prognostic factors, including the presence, and between group distribution,

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of the true prevalence of CHD, extent of coronary artery obstructions, and degree of left ventricular dysfunction.

A 13-year post trial follow-up of the Helsinki Heart Study compared CHD, cancer, and all-cause mortality among the original gemfibrozil and original placebo groups. Gemfibrozil had a 23% relative risk reduction of CHD mortality compared to placebo (p=0.05).[315]

In the double-blind Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study, 2,531 men with CHD, mean HDL-C of 31.5 mg/dL and mean LDL-C of 111 mg/dL, were randomized to gemfibrozil 1,200 mg/day or placebo.[316] The primary study outcome was nonfatal MI or death from coronary causes. At 1 year, the mean total-C was 4% lower, HDL-C was 6% higher, and TG was 31% lower in the active treatment than the placebo group; there was no between group difference in LDL-C. After a median follow-up of 5.1 years, a primary event occurred in 17.3% of patients in the gemfibrozil group and 21.7% of patients in the placebo group, a significant relative risk reduction of 22% (95% CI, 7 to 35; p=0.006). There was also a 24% relative risk reduction in the secondary composite endpoint of death from CHD, nonfatal MI, and stroke (p<0.001 compared to placebo). There were no significant differences between groups in the incidences of coronary revascularization, hospitalization for unstable angina, death from any cause, and cancer. Subsequent predefined subanalyses showed a reduced incidence in the primary outcome in patients with chronic renal insufficiency (25% relative risk reduction; p=0.02) and in patients with diabetes (32% relative risk reduction; p=0.004).[317,318]

icosapent ethyl (Vascepa)

MARINE: In a randomized, double-blind, multicenter, placebo-controlled study, 229 patients with severe hypertriglyceridemia (baseline TG levels 500 to 2,000 mg/dL) with or without background statin therapy were randomized to icosapent ethyl 4 grams daily, icosapent ethyl 2 grams daily, or placebo for 12 weeks.[319] Median TG level was 680 mg/dL, 657 mg/dL and 703 mg/dL in the 4-gram, 2-gram and placebo groups, respectively. The primary endpoint was placebo-corrected median percent change in TG from baseline to week 12. Icosapent ethyl resulted in a 33.1% reduction in the 4-gram group (p<0.001 versus placebo) and a 19.7% reduction in the 2-gram group (p=0.0051). LDL-C was not significantly increased in either group. The study found that patients with a higher baseline TG level demonstrated larger reductions. In those with a baseline TG > 750 mg/dL, the 4 gram dosage resulted in a 45.4% reduction (n=28, p=0.0001) and the 2 gram dosage resulted in a 32.9% reduction (n=28, p=0.0016). Patients who were on concomitant statin therapy had a larger decrease in TG compared to those not treated with statins (4-gram group on statins 65% reduction, p=0.0001; 2-gram group on statins 40.7% reduction, p=0.0276 compared to 4-gram group no statin 25.8% reduction, p=0.0002; 2-gram group no statins 16.4%, p=0.036). Safety profile of icosapent ethyl was similar to placebo.

ANCHOR: The efficacy and safety of icosapent ethyl were evaluated in a phase 3, double-blind, 12-week trial in high-risk statin-treated patients with residually high TG levels (≥ 200 and < 500 mg/dL) despite LDL-C control (≥ 40 mg/dL and < 100 mg/dL).[320] Patients (n=702) on a stable diet were randomized to icosapent ethyl 4 g or 2 g per day or placebo. The primary endpoint was median percent change in TG levels from baseline versus placebo. Both doses of icosapent ethyl significantly decreased TG levels by 21.5% (p<0.0001) and 10.1% (p=0.0005), respectively, and non-HDL-C by 13.6% (p<0.0001) and 5.5% (p=0.0054), respectively. Icosapent ethyl 4 g/day produced greater TG and non-HDL cholesterol decreases in patients with higher-efficacy statin regimens and greater TG decreases in patients with higher baseline TG levels. Icosapent ethyl 4 g/day also decreased LDL-C, apo B, total cholesterol, VLDL-C, lipoprotein-associated phospholipase A(2), and high-sensitivity C-reactive protein

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compared to placebo (p<0.001 for all comparisons). Icosapent ethyl was generally well tolerated, with safety profiles similar to placebo.

icosapent ethyl (Vascepa) and cardiovascular outcomes

REDUCE-IT: Icosapent ethyl effect on the risk of ischemic events was evaluated in a randomized trial in 8,179 patients on statin-therapy with triglycerides between 135 and 499 mg/dL and LDL-C between 41 and 100 mg/dL.[321] Patients also had a history of ASCVD (71%) or diabetes (29%). Patients were randomized to icosapent ethyl 4 g per day or placebo. The primary efficacy endpoint was total (first and subsequent) primary composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Median time of follow-up was 4.9 years. Overall, icosapent ethyl significantly reduced total primary endpoint events (17.2% with icosapent ethyl versus 22% placebo, respectively; hazard ratio [HR], 0.75 [95% CI, 0.68 to 0.83; p < 0.001]); each primary endpoint component was also reduced with icosapent ethyl.

lomitapide (Juxtapid)

The safety and effectiveness of lomitapide (as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available) were evaluated in a single-arm, open-label trial involving 29 adults with HoFH.[322] Current lipid-lowering therapy was maintained. Patients were counseled to follow a low-fat diet (< 20% calories from fat) and to take dietary supplements. Sixty-two percent of patients were receiving apheresis. Lomitapide dose was titrated based on safety and tolerability from 5 mg to a maximum of 60 mg daily. The primary endpoint was mean percent change in LDL-C measured at week 26. Patients remained on lomitapide for an additional year to assess long-term safety. At week 26, LDL-C was reduced by 50% (95% CI, -62 to -39; p<0.0001) from baseline; LDL-C levels remained reduced by 44% (95% CI, -57 to -31; p<0.0001) at week 56 and 38% (95% CI, -52 to -24; p<0.0001) at week 78. The most common adverse events reported were gastrointestinal symptoms. Four patients had aminotransaminase levels > 5 times the upper limit of normal, which resolved after dose reduction or temporary interruption of lomitapide.

niacin IR

The Coronary Drug Project was a 9-year, double-blind study conducted by the National Heart, Lung, and Blood Institute (NHLBI) to assess the long-term efficacy and safety of several lipid-influencing drugs (conjugated estrogens 2.5 mg or 5 mg/day, clofibrate 1.8 gm/day, dextrothyroxine 6 mg/day, niacin 3 gm/day, or placebo) in 8,341 men aged 30 to 64 years with documented MI.[323] The 2 estrogen regimens and dextrothyroxine were discontinued early because of adverse effects. No evidence of efficacy was found for the clofibrate treatment. Niacin treatment showed modest benefit in decreasing nonfatal recurrent MI but did not decrease total mortality. After a mean follow-up of 15 years, mortality from all causes in each of the drug groups, except for niacin, was similar to that in the placebo group. Study authors state that a late benefit of niacin occurred after discontinuation of the drug that may be a result of a translation into a mortality benefit over subsequent years of the early favorable effect of niacin in decreasing nonfatal recurrent MI or a result of the cholesterol-lowering effect of niacin, or both. Mortality in the niacin group was 11% lower than in the placebo group (52% versus 58.2%; p=0.0004).

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niacin ER (Niaspan)

In a double-blind, randomized, placebo-controlled trial, niacin ER 1,000 mg daily (n=87) or placebo (n=80) were added to statin therapy in 167 patients with CAD and low HDL-C (< 45 mg/dL).[324] Patients were initially started on niacin ER 500 mg and then titrated to 1,000 mg daily after 1 month. A total of 149 patients completed the study. Baseline carotid intima-media thickness (CIMT), LDL-C (mean 89 mg/dL), and HDL-C (mean 40 mg/dL) were comparable in the 2 groups. After 12 months, HDL-C increased by 21% in the niacin group. The mean CIMT increased significantly in the placebo group (p<0.001) but was unchanged in the niacin group. The difference in the CIMT progression was not statistically significant (p=0.08); however, niacin significantly reduced the rate of IMT progression in patients without insulin resistance (p=0.026). Cardiovascular event rates were similar in the small trial (3.8% in the niacin group and 9.6% in the statin-only group; p=0.2).

omega-3-acid ethyl esters (Lovaza)/simvastatin versus simvastatin

A randomized, double-blind, placebo-controlled, parallel group trial compared the combination of omega-3 acid ethyl esters 4 gm daily and simvastatin 40 mg per day with simvastatin 40 mg per day monotherapy in 254 patients with persistent high TG (200 to 499 mg/dL).[325,326] Patients were treated with 8 weeks of open-label simvastatin 40 mg daily prior to randomization to reduce LDL-C to no greater than 10% above NCEP ATP III goal and remained on this dose throughout the study. After the initial open-label phase, patients were then randomized to either omega-3-acid ethyl esters or placebo for an additional 8 weeks. Combination therapy versus monotherapy resulted in a median percentage change in TG of -29.5% versus -6.3%, respectively, (p<0.0001). The mean percentage change in HDL-C was +3.4% for combination therapy versus -1.2% for monotherapy, (p<0.05). The mean percentage change in LDL-C was +0.7% for the combination group and -2.8% for monotherapy (p=0.05).

A 16-week study randomized patients with elevated non-HDL-C > 160 mg/dL and TG ≥ 250 mg/dL, and ≤ 599 mg/dL levels to double-blind treatment with prescription omega-3-acid ethyl esters, 4 g/day, or placebo.[327] Patients also received escalating dosages of open-label atorvastatin (weeks 0-8, 10 mg/day; weeks 9-12, 20 mg/day; weeks 13-16, 40 mg/day). Omega-3-acid ethyl esters plus atorvastatin 10 mg, 20 mg, and 40 mg/day reduced median non-HDL-C levels by 40.2% versus 33.7% (p<0.001), 46.9% versus 39% (p<0.001), and 50.4% versus 46.3% (p<0.001) compared with placebo plus the same doses of atorvastatin at the end of 8, 12, and 16 weeks, respectively. Omega-3-acid ethyl esters plus atorvastatin also reduced median TC, TG, and LDL-C levels and increased HDL-C levels to a significantly greater proportion compared to placebo plus atorvastatin. At study end, percent changes from baseline LDL-C, apolipoprotein A-I, and apolipoprotein B levels were not significantly different between groups.

alirocumab (Praluent) versus placebo

ODYSSEY COMBO I was a multicenter, phase 3, randomized, double-blind, 52-week trial that evaluated the effect of alirocumab in patients with a history of ASCVD not at goal (LDL-C ≥ 70 mg/dL) or moderate chronic kidney disease (CKD) or diabetes with additional risk factors not at goal (LDL-C ≥ 100 mg/dL) despite maximally tolerated statin with or without other lipid-lowering therapy.[328] Patients with known HeFH or HoFH were excluded. Overall, 209 patients were randomized (2:1) to subcutaneous (SC) alirocumab and 107 to placebo. Eighty four percent had clinical ASCVD. Patients in the alirocumab group were initiated at a dose of 75 mg every 2 weeks with possible up-titration to 150 mg every 2 weeks at week 12 in patients whose LDL-C was still ≥ 70 mg/dL. After 24 weeks, the treatment

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difference between alirocumab and placebo in mean LDL-C percent change was 45.9% (p<0.0001). The treatment difference between alirocumab and placebo for percent change from baseline in Apo B, non-HDL-C, total cholesterol, triglyceride reductions, and HDL increase at 24 weeks were 35.8%, 37.5%, 25%, 0.6%, and 7.3%, respectively (p<0.0001 except all for triglycerides). The dose was up-titrated to 150 mg in 16% of patients treated with alirocumab for at least 12 weeks.

ODYSSEY FH I and II were both 78-week multicenter, multinational, randomized, double-blind, placebo-controlled trials in patients with HeFH not at goal (LDL-C ≥ 70 mg/dL if patient had prior CVD and ≥ 100 mg/dL if no history of CVD) despite maximally tolerated statin with or without other lipid lowering therapy.[329,330] Overall, 490 patients were assigned to alirocumab and 245 to placebo. Patients in the alirocumab group were initiated at a dose of 75 mg every 2 weeks with possible up-titration to 150 mg every 2 weeks at week 12 in patients whose LDL-C was still ≥ 70 mg/dL. After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 57.9% (p<0.0001) and 51.4% (p<0.0001) in FH I and II, respectively. In FH I, the treatment difference between alirocumab and placebo for percent change from baseline in Apo B, Non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 45.8%, 52.4%, 38.7%, 16%, and 8%, respectively (p<0.0001 for all). In FH II, the treatment differences were 39.3%, 45.7%, 32.8%, 10.9%, and 6.8%, respectively (p<0.01 for all). The dose was up-titrated to 150 mg in 43.4% and 38.6% of patients treated with alirocumab for at least 12 weeks in FH I and II, respectively.

ODYSSEY High FH, with a nearly identical trial design to FH I and II, was a 78-week trial in patients with HeFH and a baseline LDL-C ≥ 160 mg/dL. Overall, 72 patients were assigned to alirocumab 150 mg every 2 weeks and 35 to placebo.[331,332,333] After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 39.1% (p<0.0001). The treatment difference between alirocumab and placebo for percent change from baseline in apo B, non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 30.3%, 35.5%, 28.4%, 8.7%, and 3.7%, respectively (p<0.001 for all except triglycerides and HDL).

ODYSSEY LONG-TERM, a multinational, phase 3, randomized, double-blind, placebo-controlled, 18-month trial, evaluated the effect of alirocumab in non-familial hypercholesterolemia (non-FH) and HeFH ASCVD patients with high or very high cardiovascular risk not at goal (LDL-C ≥ 70 mg/dL).[334] Overall, 1,553 patients were assigned to alirocumab 150 mg every 2 weeks and 788 to placebo. Sixty-nine percent were non-FH patients with clinical ASCVD and 18% had HeFH. After 24 weeks, the treatment difference between alirocumab and placebo in mean LDL-C percent change was 61.9% (95% CI, -64.3 to -59.4; p<0.0001). The treatment difference between alirocumab and placebo for percent change from baseline in Apo B, non-HDL-C, total cholesterol, and triglyceride reductions, and HDL increase at 24 weeks were 54%, 52.3%, 37.5%, 17.3%, and 4.6%, respectively (p<0.0001).

ODYSSEY CHOICE 1 compared alirocumab 300 mg SC every 4 weeks (n=312), 75 mg every 2 weeks (n=78), and placebo (n=157) in a randomized, double-blind manner.[335,336] Included patients had inadequately controlled hypercholesterolemia and were either on maximally tolerated statin or no statin, with or without other lipid-lowering therapies. Alirocumab dosage could be adjusted to 150 mg every 2 weeks if needed after 12 weeks of therapy, based on prespecified LDL-C criteria, which occurred in approximately 20% of patient receiving alirocumab. At week 24, the treatment difference in mean percent change in LDL-C from baseline between those treated with placebo and those initially assigned to alirocumab 300 mg was -56% (97.5% CI, -62 to -49; p<0.0001); and the treatment difference between placebo and initial assignment to alirocumab 75 mg was -48% (97.5% CI, -57 to -39).

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alirocumab (Praluent) versus ezetimibe (Zetia)

The ODYSSEY COMBO II trial followed an identical study design as COMBO I but included an active comparator rather than placebo. It was a 104-week, double-blind, double-dummy, active-controlled, parallel-group, phase 3 study, comparing alirocumab to ezetimibe (n=720) in high-risk patients with ASCVD and elevated LDL-C despite maximal statin treatment (n=720).[337] Patients with known He-FH or Ho-FH were excluded. Patients were randomized to SC alirocumab 75 mg every 2 weeks or oral ezetimibe 10 mg daily, both with background statin therapy. After 24 weeks, the treatment difference between alirocumab and ezetimibe in mean LDL-C percent change was 29.8% (95% CI, -34.4 to -25.3; p<0.0001) favoring alirocumab, the primary endpoint. Secondary endpoints included percent change in LDL-C at week 12 and 52, proportion of patients reaching calculated LDL-C < 70 mmol/L at week 24, and percent change in apolipoprotein B, non-HDL-C, total cholesterol, lipoprotein A, HDL-C, fasting triglycerides, and apolipoprotein A-1 from baseline to week 24. Nearly all secondary endpoints also demonstrated superiority of alirocumab compared to ezetimibe (p<0.0001 for all endpoints excluding triglycerides). At 104 weeks, LDL-C was reduced by 49% with alirocumab compared to 17% with ezetimibe (p<0.0001), and LDL-C < 70 mg/dL was achieved by 73% of patients treated with alirocumab versus 40% treated with ezetimibe.[338] A similar overall safety profile was seen in both treatment groups at years 1 and 2.

The ODYSSEY MONO trial, a phase 3, randomized, double-blind, double-dummy study, compared alirocumab and ezetimibe in 103 moderate risk ASCVD patients that were not on any other background lipid-lowering therapy.[339] Patients with known He-FH or Ho-FH were excluded. Patients were randomized to alirocumab 75 mg SC every 2 weeks (dose could be up titrated to 150 mg if LDL-C was ≥ 70 mg/dL at week 12) or oral ezetimibe 10 mg daily. Fourteen of the 52 patients in the alirocumab treatment arm were up titrated at 12 weeks. After 24 weeks, the treatment difference between alirocumab and ezetimibe in mean LDL-C percent change was 31.6% (95% CI, -40.2 to -23; p<0.0001).

The ODYSSEY OPTIONS I study, a phase 3, 24-week, multicenter, randomized, double-blind, active-comparator study, explored the efficacy of alirocumab in 355 HeFH and non-FH ASCVD patients at high or very high cardiovascular risk not adequately controlled on atorvastatin 20 mg to 40 mg.[340] Patients were randomized to add-on alirocumab 75 mg SC every 2 weeks (up titration to 150 mg was possible based on LDL-C level and CV risk at week 12), add-on ezetimibe 10 mg/day, doubled atorvastatin dose, or a switch to rosuvastatin 40 mg (those on atorvastatin 40 mg/day only). At 24 weeks in the patient group treated with 20 mg atorvastatin at baseline, the least squares (LS) mean (standard error [SE]) percent change in LDL-C from baseline in the add-on alirocumab group was -44.1% (±4.5%), -20.5% (±4.7%) in the ezetimibe group, and -5% (±4.6%) in the atorvastatin dose doubling group (p=0.0004 alirocumab versus ezetimibe; p<0.0001 alirocumab versus atorvastatin). At 24 weeks in the patient group treated with atorvastatin 40 mg at baseline, the LS mean (SE) percent change in LDL-C from baseline was -54% (±4.3%) in the add-on alirocumab group, -22.6% (±4.3%) in the ezetimibe group, -4.8% (±4.2%) in the atorvastatin dose doubling group, and -21.4% (±4.2%) in the rosuvastatin group (p<0.0001 for all comparisons).

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alirocumab (Praluent) and cardiovascular outcomes

ODYSSEY OUTCOMES:[341,342] The impact of alirocumab on CV outcome was evaluated in the 18,924 patients on maximally-tolerated statins (90% on high-intensity therapy) who had an ACS sometime during the 12 months prior to study enrollment. Patients with residual LDL-C ≥ 70 mg/dL, non-HDL-C ≥ 100 mg/dL, or apo B ≥ 80 mg/dL after 2 to 16 weeks of intensive or maximally tolerated statin therapy were randomized (1:1) to alirocumab or placebo. Patients given alirocumab started with 75 mg every 2 weeks and the dose was increased to 150 mg every 2 weeks if LDL-C remained > 50 mg/dL (n=2,615; 805 patients switched back to 75 mg). The primary composite endpoint was overall risk reduction of major adverse cardiovascular events (MACE), which included MI, ischemic stroke, death from coronary heart disease, or hospitalization due to unstable angina. After an average of 2.8 years, the incidence of MACE was reduced by 15% in patients who received alirocumab compared to placebo-treated patients (9.5% versus 11%; HR, 0.85; 95% CI, 0.78 to 0.93; p=0.0003). There was a similar decrease in all-cause mortality (HR, 0.85; 95% CI, 0.73 to 0.98; nominal p=0.026). After a mean 2.8 years, mean LDL-C was 53.3 mg/dL in the alirocumab group and 101.4 mg/dL in the placebo group, translating to a 54.7% reduction with alirocumab.

evolocumab (Repatha) versus placebo

DESCARTES, a 52-week, phase 3, multinational, randomized, double-blind trial, evaluated the effect of evolocumab 420 mg once monthly compared to placebo (2:1) in patients 18 to 75 years of age with hyperlipidemia, an LDL cholesterol level of ≥ 75 mg/dL, and a fasting triglyceride level of ≤ 400 mg/dL who were stabilized on either diet alone, 10 mg of atorvastatin, 80 mg of atorvastatin, or 80 mg of atorvastatin plus ezetimibe (n=901).[343] The difference in LS mean reduction in LDL-C from baseline for evolocumab compared to placebo was 57% (SE, ±2.1; p<0.001) compared to placebo at 52 weeks. The treatment difference between evolocumab and placebo for percent change from baseline in Apo B, non-HDL-C, and triglycerides at 12 weeks were -44.2%, -50.3%, and -11.5%, respectively.

RUTHERFORD-2, a 12-week, multicenter, randomized, double-blind, placebo-controlled trial, evaluated the safety and efficacy of evolocumab in 329 patients with HeFH. Evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) was compared to placebo in patients aged 18 to 80 years who had a baseline LDL-C ≥ 100 mg/dL and were on a stable on statin (with or without other lipid-lowering therapies).[344] Compared with placebo, evolocumab twice monthly and once monthly reduced LDL-C by -59.2% (95% CI, -65.1 to -53.4; p<0.001) and 61.3% (95% CI, -69 to -53.6; p<0.001), respectively, at 12 weeks. The treatment difference between evolocumab and placebo for percent change from baseline in Apo B, non-HDL-C, and triglycerides at 12 weeks were -49.1%, -54.8%, and -19.6% in the every 2 week group and -49.4%, -55%, and -11.6% in the once monthly group, respectively (all p<0.0001 excluding triglycerides in the monthly treatment group [p=0.0214]).

TESLA (Part B), a 12-week, phase 3, multinational, randomized, double-blind, placebo-controlled trial, evaluated the efficacy of evolocumab in 49 patients with HoFH.[345] Patients aged 13 to 80 years who had a baseline LDL-C ≥ 130 mg/dL and were on lipid-lowering therapies, but not on lipid-apheresis therapy, were randomized 2:1 to evolocumab 420 mg once monthly or placebo. Compared with placebo, evolocumab reduced LDL-C by 30.9% (95% CI, -43.9 to -18; p<0.0001) at 12 weeks. The treatment difference between evolocumab and placebo for percent change from baseline in Apo B, HDL-C, and triglycerides were -23.1%, -0.1%, and 0.3, respectively (p value significant for Apo B only [p=0.0007]).

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The GLACOV (Global Assessment of Plaque ReGression with a PCSK9 AntibOdy as Measured by IntraVascular Ultrasound) study randomized 968 patients with atherosclerosis to evolocumab (420 mg once per month) or placebo as add-on to background statin therapy.[346] The addition of evolocumab produced a significantly greater atheroma regression as measured by percent atheroma volume (PAV) than statin therapy alone after 76 weeks of therapy; PAV +0.05% with placebo, PAV -0.95% with evolocumab (95% CI, −1.8 to −0.64; p<0.001). The secondary measure of total atheroma volume (TAV) decreased by 0.9 mm^3 with placebo and 5.8 mm^3 with evolocumab (95% CI, −7.3 to −2.5; p<0.001). Plaque regression was seen in 64.3% compared to 47.3% of patients on evolocumab plus a statin versus statin therapy alone, the difference is significant (difference 17% [95% CI, 10.4 to 23.6]; p<0.001).

FOURIER, a double-blind, trial enrolled 27,564 adults with established CVD and LDL-C ≥ 70 mg/dL and/or non-HDL-C ≥ 100 mg/dL despite moderate to high intensity statin therapy.[347] Patients were randomized (1:1) to SC evolocumab (140 mg every 2 weeks or 420 mg once monthly) or placebo. The primary composite endpoint was time to first occurrence of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The primary endpoint was significantly lower with evolocumab compared to placebo (4.5% versus 5.2%; HR, 0.85; 95% CI, 0.79 to 0.92; p<0.0001). This was primarily driven by the decreases in the times to first MI (HR, 0.73; 95% CI, 0.65 to 0.82), first stroke (HR, 0.79; 95% CI, 0.66 to 0.95), and first coronary revascularization (HR, 0.78; 95% CI, 0.71 to 0.86).

evolocumab (Repatha) versus ezetimibe (Zetia)

LAPLACE-2, a 12-week, randomized, double-blind trial, evaluated the effect of evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) compared to placebo or ezetimibe 10 mg/day in 1,899 patients with primary hypercholesterolemia and mixed dyslipidemia stabilized on moderate or high-intensity statin therapy.[348] At the mean of 10 and 12 weeks, evolocumab every 2 weeks reduced LDL-C levels by 66% (95% CI, 58 to 73) to 75% (95% CI, 65 to 84) and monthly by 63% (95% CI, 54 to 71) to 75% (95% CI, 67 to 83) compared to placebo in the moderate and high intensity statin groups. Ezetimibe reduced LDL-C values by 17% to 24% from baseline, evolocumab (every 2 weeks) reduced LDL-C values by 61% to 62% (p<0.001 versus ezetimibe), and evolocumab (monthly) reduced LDL-C values by 62% to 65% (p<0.001 versus ezetimibe).

MENDEL-2, a randomized, controlled, phase 3 clinical trial, studied evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) compared to either ezetimibe 10 mg/day or placebo as monotherapy in 614 patients, 18 to 80 years of age, with primary hypercholesterolemia, fasting LDL-C ≥ 100 mg/dL and < 190 mg/dL, and Framingham risk scores ≤ 10%.[349] At 12 weeks, average LDL-C decreased by a mean of 57% (95% CI, -59.5 to -54.6) with evolocumab every 2 weeks, 56.1% (95% CI, -58.3 to -53.9) with evolocumab once monthly, 0.1% to 1.3% (95% CI, -3.2 to 3.4; and 95% CI, -4.4 to 1.7, respectively) in placebo groups 1 and 2, and 17.8% to 18.6% (95% CI, -21 to -14.5; and 95% CI, -21.6 to -15.5, respectively) in ezetimibe groups 1 and 2 (p<0.001 evolocumab versus placebo and ezetimibe). These reductions were also significant for the mean of week 10 and week 12 compared to placebo and ezetimibe (p<0.001), the other co-primary endpoint. Significant differences were found when comparing both dosing schedules of evolocumab to placebo and ezetimibe in the following lipid parameters (apolipoprotein B, lipoprotein a, non-HDL-C, and HDL-C [p<0.02 for all comparisons]).

GAUSS-2, a 12-week, double-blind, randomized controlled trial, studied evolocumab (dosed either 140 mg every 2 weeks or 420 mg once monthly) compared to ezetimibe 10 mg/day in 307 patients

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with hyperlipidemia diagnosed with statin intolerance.[350] The mean percent change in LDL-C from baseline at week 12 was -55.3% to -56.1% with evolocumab and -16.6% to -19.2% with ezetimibe (treatment difference -36.9 to -38.7; p<0.001 for both comparisons). The mean percent change in LDL-C from baseline at week 10 and 12 was -52.6% to -56.1% with evolocumab and-15.1% to -18.1% with ezetimibe (treatment difference -37.6 to -38.1; p<0.001 for both comparisons). Significant differences were also seen in some secondary endpoints: apolipoprotein B, lipoprotein a, and LDL-C < 70 mg/dL (p<0.001), but not in HDL-C or apolipoprotein A-1.

GAUSS-3, a double-blind, randomized cross-over study, enrolled 491 adults with uncontrolled LDL-C and an intolerance to 2 or more statins.[351] After a 4-week washout period when all lipid-lowering agents were discontinued, patients entered the crossover phase A. Patients were randomized to atorvastatin 20 mg daily or placebo for 10 weeks, then entered a 2 week wash-out period, followed by a crossover to the alternative therapy for 10 weeks. A total of 199 patients (42.6%) experienced muscle-related adverse effects while on atorvastatin but not placebo and continued on to the 24-week, phase B portion of the study. In addition, 19 patients with a documented history of CK elevation > 10 x ULN with muscle symptoms while on statin therapy entered the study directly at phase B. In this phase, patients received either evolocumab SC 420 mg monthly or ezetimibe 10 mg daily, with corresponding opposite matching-placebo. Coprimary endpoints were mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels and from baseline to week 24 levels. For the mean of weeks 22 and 24, there was a mean change in LDL-C by −16.7% (95% CI, -20.5 to -12.9) for ezetimibe and -54.5% (95% CI, -57.2 to -51.8) for evolocumab. Further, with ezetimibe, at week 24 the mean percent change in LDL-C was −16.7% (95% CI, −20.8 to −12.5); with evolocumab it was −52.8% (95% CI, −55.8 to −49.8). Muscle symptoms were experienced by 28.8% of patients treated with ezetimibe and 20.7% with evolocumab.

evolocumab (Repatha) and cardiovascular outcomes and cognitive effects

In the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) double-blind study, 27,564 patients with ASCVD and LDL-C ≥ 70 mg/dL or a non-high density lipoprotein cholesterol ≥ 100 mg/dL, who were on optimal statin therapy, were randomly assigned to evolocumab (140 mg every 2 weeks or 420 mg monthly) or placebo subcutaneous injections.[352] Ezetimibe use was allowed but was infrequent. Median follow-up was 26 months. At 48 weeks, there was a least-squares mean percentage reduction in LDL-C levels of 59% with evolocumab compared with placebo. The primary endpoint, a composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, occurred 15% less often with evolocumab (9.8%) than with placebo (11.3%). The key secondary composite endpoint of CV death, MI, or stroke occurred 20% less often with evolocumab versus placebo (5.9% versus 7.4%). In addition, EBBINGHAUS, a substudy that included 1,204 patients from the FOURIER study who had baseline and follow-up cognitive testing, revealed that there were no significant changes from baseline in cognitive function, as measured by spatial working memory strategy index (SWMsi) of executive function, in patients treated with either, evolocumab or placebo.[353]

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META-ANALYSES

Fibric acids were compared to niacin in a meta-analysis evaluating lipid parameter effects and risk reductions for major cardiac events.[354] Data from 53 trials (n=16,802) using fibric acids and 30 trials (n=4,749) using niacin were included in the meta-analysis. Fibric acids included agents which have never been available in the U.S., in addition to gemfibrozil and fenofibrate. Niacin products included immediate-, sustained-, and extended-release formulations. Reductions in LDL-C and TG were 36% and 8% for fibric acids and 20% and 14% for niacin, respectively. Increases in HDL-C were 10% and 16% for fibric acids and niacin, respectively. Relative risk reduction for major cardiac events was 25% and 27% for fibric acids and niacin, respectively.

A systematic review searched the literature to identify randomized, double-blind, placebo-controlled trials examining the effect of fibrates on lipid profiles or cardiovascular outcomes.[355] Fibrates were associated with greater reductions in total cholesterol (range: -101.3 mg/dL to -5 mg/dL) and TG (range: -321.3 mg/dL to -20.8 mg/dL), and a greater increase in HCL-C (range: +1.1 mg/dL to +17.9 mg/dL), compared to placebo, in all trials. Although not consistently, fibrates tended to be associated with a greater reduction in LCL-C (range: -76.3 mg/dL to +38.7 mg/dL) than placebo. Fibrates were better than placebo at preventing nonfatal MI (OR, 0.78; 95% CI, 0.69 to 0.89), but not all-cause mortality (OR, 1.05; 95% CI, 0.95 to 1.15).

A systematic review and meta-analysis searched for prospective randomized placebo-controlled fibrate trials with effect on CV outcomes published between 1950 and March 2010.[356] Medline, Embase, and the Cochrane Library were searched. Summary estimates of relative risk (RR) reductions were calculated with a random effects model. Outcomes analyzed included major CV events, coronary events, stroke, HF, coronary revascularization, all-cause mortality, CV death, non-vascular death, sudden death, new onset albuminuria, and drug-related adverse events. Eighteen trials with 45,058 patients were identified, including 2,870 major CV events, 4,552 coronary events, and 3,880 deaths. Fibrate therapy produced a 10% RR reduction (95% CI, 0 to 18) for major CV events (p=0.048) and a 13% RR reduction (95% CI, 7 to 19) for coronary events (p<0.0001), but had no benefit on stroke (−3%; 95% CI, −16 to 9; p=0.69). There was no effect of fibrate therapy on the risk of all-cause mortality (0%; 95% CI, −8 to 7; p=0.92), CV mortality (3%; 95% CI, −7 to 12; p=0.59), sudden death (11%; 95% CI, −6 to 26; p=0.19), or non-vascular mortality (−10%; 95% CI, −21 to 0.5; p=0.063). Fibrates reduced the risk of albuminuria progression by 14% (95% CI, 2 to 25; p=0.028). Serious drug-related adverse events were not significantly increased by fibrates (RR 1.21; 95% CI, 0.91 to 1.61; p=0.19), although increases in serum creatinine concentrations were common (1.99; 95% CI, 1.46 to 2.7; p<0.0001).

A meta-analysis of 11 randomized trials with 6,616 patients found niacin significantly reduced major coronary events (relative OR, 25%; 95% CI, 13 to 35), stroke (25%; 95% CI, 8 to 41), and any CV events (27%; 95% CI, 15 to 37).[357] In comparison with the non-niacin group, more patients in the niacin group showed regression of coronary atherosclerosis (relative increase 92%; 95% CI, 39 to 67), but the rate of patients with progression decreased by 41% (95% CI, 25 to 53). Similar effects of niacin were found on carotid intima thickness with a weighted mean difference in annual change of -17 µm/year (95% CI, -22 to -12).

A systematic review and meta-regression analysis was performed for fibrates, niacin, and marine-derived omega-3 fatty acids.[358] Randomized controlled trials (RCTs) reporting major vascular events were selected for inclusion (24 nonstatin therapy trials and 25 statin therapy trials). Overall, the RCTs showed lowering of TGs was associated with a decreased risk for major vascular events, even with

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adjustments for reduction in LDL-C; however, the observed effect was less pronounced than seen with LDL-C reduction. The risk ratio (RR) for major vascular events associated with absolute reduction in lipid parameters were as follows per 1-mmol/L reduction in the lipid parameter: 0.80 (95% CI, 0.76 to 0.85; p<0.0001) for LDL-C, 0.84 (95% CI, 0.75 to 0.94; p=0.0026) for TG. The association between TG reduction and reduction in major vascular events was weaker once findings from the REDUCE-IT study (Reduction of CV Events with Icosapent Ethyl-Intervention Trial) were removed, which had results that were an outlier to the other studies. After removal of the REDUCE-IT study, the RR per 1-mmol/L reduction in LDL-C was 0.79 (95% CI, 0.76 to 0.83; p<0.0001) and 0.91 (95% CI, 0.81 to 1.006; p=0.06) for each per 1-mmol/L (0.96 per 40 mg/dL) reduction in TGs.

Effects on Lipids for Selected Agents[359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410]

While outcomes data are lacking for many of the non-statin lipotropics, the effects of these agents on the lipid profile are well documented and may serve as an indirect indicator of the efficacy. Conditions and populations in clinical trials may vary.

Effects on Lipids

Drug	total-C (% change)	LDL-C (% change)	HDL-C (% change)	TG (% change)
ACL Inhibitor bempedoic acid (Nexletol)	-11 to -18	-17 to -29	-4.5 to -5.9	-9.2 +0.4
ACL Inhibitor/Cholesterol Absorption Inhibitor bempedoic acid/ezetimibe (Nexlizet)	-27	-38	nr	nr
Bile Acid Sequestrants cholestyramine, colestipol (Colestid), colesevelam (Welchol)	-9 to -13	-12 to -30	+3 to +9	0 to +25
Cholesterol Absorption Inhibitors ezetimibe (Zetia)	-12 to -14	-13 to -20	+1 to +5	-5 to -11
Fibric Acids fenofibrate (Antara, Fenoglide, Lipofen, Tricor, Triglide) gemfibrozil (Lopid)	-4 to -26	-27 to +9	+ 6 to +18	- 29 to -54
fenofibric acid (Fibricor)	-9 to -22	-31 to +45	+10 to +23	- 24 to -54
fenofibric acid (Trilipix)	-12	-5	+16	-31
lomitapide (Juxtapid)	-36	-40	-7	-45
niacin ER (Niaspan)	-3 to -10	-14 to +2	+18 to +26	-13 to -29
niacin IR (Niacor)	-10 to -20	-10 to -20	+20 to +35	-30 to -70
omega-3-acid ethyl esters (Lovaza)	-10	+45	+9	-45
icosapent ethyl (Vascepa)	-7	-5	-4	-27
alirocumab (Praluent)	-27 to -38	-43 to -61	+4 to +9	-6 to -16
evolocumab (Repatha)	-17 to -42	-22 to -65	+4 to +9	-5 to -20

nr = not reported

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SUMMARY

The preponderance of outcomes data supports the use of statins as the primary agents for low-density lipoprotein cholesterol (LDL-C) reduction therapy and for primary and secondary prevention of coronary heart disease. According to the 2018 American College of Cardiology (ACC) and the American Heart Association (AHA) practice guidelines for the management of blood cholesterol emphasizes lifestyle therapies to reduce atherosclerotic cardiovascular disease (ASCVD) risk. In addition to the 10-year ASCVD risk score, the ACC/AHA advise consideration of risk-enhancing factors, such as family history of premature ASCVD, persistent LDL-C ≥ 160 mg/dL, persistent triglycerides ≥ 175 mg/dL, metabolic syndrome, chronic kidney disease (CKD), history of preeclampsia or premature menopause, chronic inflammatory disorders, and high-risk ethnic groups, among others, when considering anti-lipid therapy. While non-statin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD, they (e.g., ezetimibe, PSCK9 inhibitors) may be added to maximally tolerated statin therapy to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C.

The 2012 Endocrine Society guideline on the evaluation and treatment of hypertriglyceridemia recommends drug therapy to reduce the risk of pancreatitis in patients with severe and very severe hypertriglyceridemia; a fibrate is considered a first-line treatment. For patients with moderate to severe hypertriglyceridemia, fibrates, niacin, and omega-3 fatty acids alone or in combination with statins may be considered. Statins should not be used alone for severe or very severe hypertriglyceridemia; however, statins may be useful for the treatment of moderate hypertriglyceridemia to modify cardiovascular disease risk. The 2020 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) consensus statement algorithm for the management of dyslipidemia and prevention of CV disease also addresses treatment of hypertriglyceridemia. For patients with hypertriglyceridemia who do not have established ASCVD or diabetes with ≥ 2 risk factors and are not at the TG goal of < 150 mg/dL with statin therapy, then a fibrate, omega-3 fatty acid, or niacin can be considered. In order to decrease the potential for acute pancreatitis, all patients with severe hypertriglyceridemia (> 500 mg/dL) should receive a fibrate, prescription-grade omega-3 fatty acid, and/or niacin.

The bile acid sequestrant, cholestyramine, has been shown to reduce major coronary events and coronary heart disease deaths. The bile acid sequestrants are effective in lowering LDL-C and a small increase in high-density lipoprotein cholesterol (HDL-C). Effect on decrease in triglycerides levels has been reported between 0% and 25%. Bile acid sequestrants can be used in combination with statins. Patients generally have poor compliance to bile acid sequestrants because of the side effect profile. Colesevelam (Welchol) provides an alternative to cholestyramine and colestipol with a potential lower incidence of gastrointestinal effects. Colesevelam has also been studied in pediatrics ages 10 to 17 years of age with heterozygous familial hypercholesterolemia. In patients with type 2 diabetes mellitus, colesevelam only provides modest hemoglobin A1c (HbA1c) reductions (-0.5%) and can provide an option in patients who are almost at HbA1c goal who also require lipid lowering. ACC down-graded their recommendations on use of bile acid sequestrants to use only as a secondary alternative in patients intolerant to ezetimibe.

Gemfibrozil (Lopid) has demonstrated reductions in risk of coronary heart disease primarily in subsets of patients with high triglycerides, low HDL-C, and characteristics of metabolic syndrome. In the FIELD study in patients with type 2 diabetes mellitus, fenofibrate was not shown to reduce coronary heart

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disease morbidity and mortality. Fenofibrate produced a nonsignificant reduction in the primary endpoint of coronary events. Non-fatal MI and total cardiovascular events were significantly reduced, but all-cause mortality was not. In the ACCORD trial, combination of fenofibrate and simvastatin did not reduce rates of cardiovascular disease, compared to simvastatin monotherapy. The ACCORD findings do not support the routine use of combination fenofibrate and statin therapy, over statin therapy alone, to reduce cardiovascular risk in most patients with type 2 diabetes that are at high risk for cardiovascular disease. Fibric acids lower triglycerides levels and raise HDL-C levels to a greater extent than do the statins, but fibrates as a group have less favorable effects on clinical CV outcomes. Depending on the specific type of dyslipidemia, the fibric acids may lower total cholesterol and LDL-C, although not as significantly as the statins. The fibric acids should be considered as an alternative agent to the statins for specific lipid disorders or can be used as add-on therapy with caution considering the increased risk of rhabdomyolysis. Fenofibrate is less likely to interact with statins compared to gemfibrozil. The FDA has removed the indication of fenofibric acid (Trilipix) use in combination with a statin; however, the use of fibrates with statins is still common in practice.

Niacin has been shown to reduce major coronary events. Compared to immediate-release niacin (Niacor), niacin extended-release (Niaspan) may increase compliance and reduce the incidence of flushing. In the AIM-HIGH study, there was no incremental benefit on cardiovascular risk reduction (including myocardial infarctions and stroke) when niacin extended-release was added to simvastatin therapy versus simvastatin therapy alone. In addition, a small, unexplained, increase in the rate of ischemic stroke was observed in the simvastatin plus extended-release niacin arm compared to simvastatin alone. The FDA has removed the indication for niacin extended-release (Niaspan) in combination with simvastatin or lovastatin. Over-the-counter (OTC) preparations of niacin are not federally regulated and, therefore, may lack nicotinic acid or be associated with an increased risk of hepatotoxicity.

Ezetimibe (Zetia) is the only available cholesterol absorption inhibitor. It inhibits intestinal absorption of both dietary and biliary cholesterol by blocking its transport at the brush border of the small intestine. Ezetimibe reduces LDL-C, both when given alone and in combination with a statin. In addition, the IMPROVE-IT study reported lower cardiovascular mortality and morbidity when ezetimibe was added to statin (simvastatin) therapy as compared to a statin alone. Ezetimibe has been studied in pediatrics ages 10 to 17 years of age with heterozygous familial hypercholesterolemia.

Lomitapide (Juxtapid) is approved for use in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to a low-fat diet and other lipid-lowering treatments. These agents inhibit the production of apolipoprotein B which leads to a reduction in LDL-C concentration. The safety and effectiveness of lomitapide has not been established in patients with hypercholesterolemia who do not have HoFH.

Omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) reduce triglycerides in patients with very high triglycerides (> 500 mg/dL). Although eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have shown reduction in major coronary events, the specific formulations for omega-3-acid ethyl esters (Lovaza) and icosapent ethyl (Vascepa) were not used. Several forms of omega-3 fatty acids are sold OTC; however, Lovaza has a high concentration of EPA and DHA in a single capsule. Both twice daily, low capsule count omega-3-acid ethyl esters and icosapent ethyl do not increase the risk of rhabdomyolysis in combination with statins. Icosapent ethyl contains only EPA, while omega-3-acid ethyl esters contain both EPA and DHA. A 2017 Science Advisory by the AHA states that omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable in patients with coronary heart

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disease (CHD) to reduce CHD-related mortality. Based on findings of the REDUCE-IT trial, icosapent ethyl has received FDA approval as adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adults with elevated TG levels (≥ 150 mg/dL) and established CVD or diabetes mellitus and ≥ 2 additional risk factors for CVD.

Alirocumab (Praluent) and evolocumab (Repatha) are agents in a newer class of drugs, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Both have demonstrated significant efficacy in regard to LDL-C lowering. Both agents are indicated for use in patients with HeFH or CVD. Evolocumab is also indicated in patients with HoFH. The AHA advises that PCSK9 inhibitors can be added to high-intensity statin plus ezetimibe therapy in patients with familial hypercholesterolemia when dual therapy does not result in desired LDL-C goal after 3 months of adherent therapy. The American College of Endocrinology (ACE) and the American Association of Clinical Endocrinologists (AACE) have also included PCSK9 inhibitors in their algorithm for use in patients with T2DM as an option as add-on to statins in patients with clinical ASCVD who are not at goal with maximally tolerated statin or in those with familial hypercholesterolemia (FH). Alirocumab and evolocumab may be dosed subcutaneously once every 2 weeks. Evolocumab is also available as a once-monthly 420 mg dose administered either as 3 consecutive SC injections (all within 30 minutes) or with the single-use Pushtronex system that delivers the 420 mg SC dose over 9 minutes. Recently, the FOURIER and ODYSSEY OUTCOMES studies reported a positive effect on CV outcomes as evidenced by a 15% reduction in the composite of CV outcomes when evolocumab or alirocumab were added to optimal statin therapy.

Bempedoic acid (Nexletol) is a first-in-class, oral adenosine triphosphate-citrate lyase (ACL) inhibitor. In February 2020, bempedoic acid and bempedoic acid/ezetimibe (Nexlizet) both received FDA approval to be used as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C. Bempedoic acid and bempedoic acid/ezetimibe have not yet been incorporated into clinical guidelines; however, these agents offer another option for those requiring additional cholesterol lowering therapy for patients who are not at goal with diet and maximally tolerated statin therapy. PCSK9 inhibitors have demonstrated superior reductions in LDL-C compared to bempedoic acid, although these were not comparative clinical trials. While bempedoic acid is not associated with myalgias, as seen with statin therapy, it does carry risks for hyperuricemia and tendon rupture. Although AACE/ACE maintains statins as primary therapy, their 2020 consensus statement algorithm recommends treatment intensification with the addition of other LDL-C lowering agents (e.g., PCSK9 inhibitors, ezetimibe, colesevelam, or bempedoic acid) as needed to reach treatment goals.

Each class of non-statin lipotropics provides a unique option for use in patients who cannot reach target lipid levels on statin monotherapy or who do not tolerate statins. While there are not outcomes data for each class, their effects on lipids profiles are clearly substantiated.

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